**Toxoplasma Retinochoroiditis**

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**Introduction**

Toxoplasmosis is caused by an obligate intracellular parasite, Toxoplasma Gondii. It has a universal distribution and a high serologic prevalence in all countries but the incidence of Toxoplasma induced disease is much lower. It is the most common cause of posterior uveitis accounting for over 80% of the cases in some regions.

**Clinical Features**

Toxoplasma infection in humans can be described under 4 headings: Congenital, Acquired, Toxoplasmosis in immunocompromised host and Ocular.

**Congenital Toxoplasmosis**

Congenital infection results from transplacental transmission of Toxoplasma gondii. Only maternal infection acquired just before or during gestation endangers the fetus and not chronic maternal infection. The incidence and severity of congenital infection vary with the timing of maternal infection. In the 1st trimester the incidence of fetal infection is only around 15-20% but it can result in abortion or still birth. In the 3rd trimester the incidence of fetal infection is approximately 40% but it commonly results in subclinical infection with few cases of clinical congenital toxoplasmosis.

Clinical manifestations of congenital toxoplasmosis consists of retinochoroiditis, hydrocephalus, microcephaly, cerebral calcification, seizures, organomegaly, jaundice, rashes and fever. The spectrum of clinical disease in congenital toxoplasma infection include Ocular lesions - 76%, Neurologic disorders - 51%, Intracranial calcifications - 32% and Hydrocephalus or Microcephaly – 26%.

Over 80% of congenitally infected infants develop ocular disease by adolescence. Retinochoroiditis is the commonest ocular lesion. 20-40% of congenital cases are bilateral. A punched out macular cicatrical lesion with central necrotic area associated with overlying vitreous inflammation is characteristic. Reactivation of congenital toxoplasmosis occurs as satellite lesion wherein new lesions develop at the margin of the old scar. Because of the end artery anatomy of fetal macular circulation there is a predilection for posterior pole in congenital toxoplasmosis.

The diagnosis of congenital toxoplasmosis is based on the classic triad of convulsions, cerebral calcification and chorioretinitis(3Cs). Anti toxoplasma IgM antibodies are found in 75% of infants with congenital toxoplasmosis. But fetal IgM antibodies may not be found at birth in 25% cases owing to delayed antibody synthesis by the fetus. In children with mild infection, retinochoroidal scars may be found on routine ophthalmoscopic examination for evaluation of squint or following school screening.

**Acquired Toxoplasmosis**

Typically, about 70% of immunocompetent patients who acquire toxoplasmosis are completely symptom free. 10-20% of cases can be symptomatic with acute flu like illness associated with fever, lymphadenopathy, malaise, myalgia and papulomacular rash sparing palms and soles, hepatosplenomegaly and atypical lymphocytosis. In the immunocompetent host, the disease is self limited and benign. The most common manifestation is lymphadenopathy. However in immunocompromised hosts life threatening encephalitis, pneumonitis or myocarditis may develop. Recent data suggests that most of the ocular diseases are secondary to acquired toxoplasmosis and not due to reactivation of congenital disease. Contact with pets such as dogs and cats, ingestion of raw undercooked meat or contaminated water are the common sources of infection in acquired Toxoplasmosis.

**Toxoplasmosis in immunocompromised hosts**

Immunocompromised patients are at increased risk for developing acute toxoplasmosis. The disease may be caused by reactivation of a chronic infection or it may be an acquired infection. Toxoplasmosis in these individuals carries a poor prognosis and can lead to life threatening encephalitis, pneumonitis or myocarditis. Ocular toxoplasmosis in AIDS patients is relatively uncommon and occurs in only about 1% to 3%, and of these cases, up to 25% are thought to be the result of a newly acquired infection. When Toxoplasma
Retinochoroiditis occurs in AIDS patients, it is frequently associated with encephalitis. 25% of AIDS patients with ocular toxoplasmosis also have intracranial involvement.

Retinochoroiditis in these patients is usually atypical and it tends to be more severely necrotizing, bilateral, multifocal, perivascular in location and not adjacent to an old scar. Ocular inflammation is variable and depends on the patient’s lymphocyte count at the time of active disease.

In general, AIDS patients who develop toxoplasmosis are still able to mount enough of a cellular immune response to produce the clinical findings of vascular sheathing, prominent vitritis, and intense anterior uveitis. Ocular toxoplasmosis may follow a devastating course in AIDS patients, with inflammation extending into the orbit, causing orbital cellulitis or panophthalmitis.

The differential diagnosis may include cytomegalovirus (CMV) retinitis, syphilitic retinitis, and progressive outer retinal necrosis (POR). However, toxoplasma does not have the significant retinal hemorrhages seen in CMV retinitis, nor is the retinitis limited to the outer retinal layers, as in POR.

Serologic diagnosis of toxoplasmosis in the immuno-compromised patient is often difficult due to the depressed antibody response in which IgM antibody and the rise in IgG antibody titre may not be detectable.

**Ocular Toxoplasmosis**

Ocular Toxoplasmosis most often presents as focal necrotizing retinitis generally associated with vitritis and granulomatous anterior uveitis. Less commonly ocular infection may present as papillitis or neuroretinitis. The first attack of ocular toxoplasmosis is typically in the second decade. 75% cases occur between 10 and 35 years.

Retinochoroiditis often presents as a focus of retinitis involving inner retinal layers. It appears as a whitish fluffy lesion with surrounding retinal edema. Retina is the primary site of infection. The choroid and sclera may be involved secondarily. Classically the active lesion is seen adjacent to an old inactive scar, the so called satellite lesion. After a variable time period, pigmentation occurs, particularly at the margins of the lesion. The time required for a chorioretinal lesion to heal varies, depending on the size of the lesion, the treatment delivered and the immunologic condition of the host. A healed Toxoplasma scar typically has well-defined borders with central retinochoroidal atrophy and peripheral pigment epithelial hyperplasia. In the atrophic central area, either choroidal vessels or bare sclera may be observed. Healing Toxoplasma lesions may be complicated by proliferative vitreoretinopathy, retinal gliosis, vascular shunts, and choroidal neovascular membranes. Traction bands are also frequent, and they usually link an old scar to the optic disc (Franceschetti’s syndrome).

Vitreitis is usually marked and is present in nearly all cases. When extensive vitreitis is present, the active retinal lesion may have the classic ophthalmoscopic appearance of a headlight in the fog. Vitreous involvement may occur as a localized or diffuse exudate, inflammatory cells, pigment, or hemorrhage. Vitreous opacities tend to be slowly reabsorbed and may persist for years after complete resolution of the retinal lesion. When there is severe and prolonged vitreous
involvement, vitreous contraction, posterior vitreous detachment, or even retinal detachment may occur.

Vascular involvement, which may occur either in the vicinity of the active lesion or in the distant retina, typically consists of a diffuse or segmental vasculitis produced by antigen-antibody complex deposition in the vessel wall, as well as localized mononuclear cell infiltrates. The vasculitis involves primarily the veins, but arterial involvement is also common. The vasculitis may result in complications such as retinal hemorrhage, vascular obstruction, vascular shunting, and even neovascularisation. Kyrieleis arterialitis (the presence of exudates or periarterial plaques not associated with leakage or vascular obstruction) is also observed as an inflammatory response in ocular toxoplasmosis.

The anterior segment can also be involved with a granulomatous or non granulomatous inflammatory reaction. This process is believed to develop as a result of a hypersensitivity reaction to Toxoplasma antigen. The iridocyclitis is usually transient, but prompt therapy is necessary to avoid complications.

Signs and symptoms of ocular toxoplasmosis vary with age. Children are generally referred to the ophthalmologist with complaints of decreased visual acuity, strabismus, nystagmus, leukocoria, choroidal coloboma, and microphthalmia. Adolescents and adults typically complain of blurred vision and floaters (>90%). Decreased vision can be because of retinochoroiditis involving the macula or due to vitreitis. Patients can also complain of metamorphopsia due to macular edema.

**Toxoplasma papillitis**

Few patients develop foci of inflammation within or directly adjacent to optic nerve head. The presence of inactive toxoplasma scars in the retina gives a clue to the diagnosis of toxoplasma papillitis. Toxoplasma infection can also cause neuroretinitis characterized by optic nerve head edema, stellate macular exudation and vitreitis. Toxoplasmic neuroretinitis can be associated with or without inactive chorioretinal scars.

Atypical patterns like vasculitis resembling Frosted Branch Angitis, peripheral necrotizing retinitis without adjacent pigmented retinal scars, peripheral lesions simulating the snow-banking of pars planitis, fuchs’ heterochromic iridocyclitis like picture, unilateral pigmented retinopathy like retinitis pigmentosa as a sequela of chronic recurrent ocular toxoplasmosis all have been has been reported. Such atypical lesions are seen in elderly individuals and in those with underlying immunodeficiency due to various causes.

**Recurrence**

Recurrences are attributed to release of live parasites from tissue cysts that remain in the retina after initial infection. Recurrences become increasingly uncommon for an individual patient over time, eventually resulting in extended periods without active disease. Although seroprevalence increases with age, recurrences occur predominantly in adolescents and young adults. There is no association between recurrences and the treatment opted, congenital infections (vs postnatally acquired infections), primary lesions (vs recurrent lesions), size of lesions, or antibody levels.

Risk of recurrence is modulated by the interplay between age at initial infection and age at the time of the episode under consideration. After the first attack the mean recurrence rate within 3 yrs is about 50% and five years is about 80% and the average number of recurrent attacks per patient is 2.7.

**Complications**

Secondary glaucoma is the most common complication. Others include cataract, retinal detachment, CNVM, vitreous hemorrhage, epiretinal membrane formation, macular edema and optic atrophy.

**Differential Diagnosis**

Congenital toxoplasmosis of the newborn must be differentiated from the other infectious diseases of the TORCH group (rubella, cytomegalovirus, and herpes simplex virus as well as other congenital infectious diseases that may simulate toxoplasmosis, such as syphilis, tuberculosis, and AIDS). Important ocular entities that may be confused with congenital toxoplasmosis include coloboma, persistent hyperplastic primary vitreous, and retinoblastoma.

Recurrent Toxoplasma lesions adjacent to retinochoroidal scars may resemble serpiginous choroiditis. However, in serpiginous choroiditis there is usually helicoid chorioretinal scars occurring in the peripapillary area and no significant inflammatory reaction of the anterior segment or vitreous.

Toxo lesions should be differentiated from other forms of retinitis like candidiasis, CMV retinitis and acute retinal
necrosis. Toxo is usually active in only one eye where as candidiasis is usually bilateral with multifocal smaller fluffy retinal lesions in early stage which break into the vitreous later causing endophthalmitis. CMV retinitis is a slowly spreading retinal lesion with hemorrhages at the advancing border. The satellite phenomenon is not seen in CMV. Retinal hemorrhages are not common in toxoplasma. In acute retinal necrosis(ARN) there are confluent areas of retinal necrosis in the periphery which gradually spreads to the centre along with occlusive vasculopathy involving both arteries and veins associated with intense vitreous reaction.

Punctate outer retinal toxoplasmosis must be distinguished from acute posterior multifocal placoid pigment epitheliopathy (APMPPE), punctate inner choroidopathy (PIC), and multifocal choroiditis, as well as diffuse unilateral subacute neuroretinitis (DUSN). In cases of Toxoplasma neuroretinitis, other causes of neuroretinitis, such as cat scratch disease and viral syndromes, must be excluded. Toxoplasma neuritis should be differentiated from the optic neuritis associated with sarcoidosis and CMV.

**Diagnosis**

The diagnosis of ocular toxoplasmosis is usually based on clinical findings. Laboratory tests are helpful to support the diagnosis when the ocular manifestations are atypical. The diagnosis should not depend solely on serologic tests because the antigen load of a small, active lesion in one eye may not be enough to stimulate elevated systemic antibody titers. In ocular toxoplasmosis there can be poor correlation between the serum levels of antibody and active disease. It is not unusual to find low or negative IgM and IgG titers in patients with acute symptomatic or recurrent ocular toxoplasmosis. For these reasons, undiluted serum should be used for the detection of anti-Toxoplasma antibody in ocular toxoplasmosis.

In patients with atypical lesions, positive serology suggests only a presumptive diagnosis, because there is a high prevalence of anti-Toxoplasma antibodies in the human population. In patients whose diagnosis is unclear, the determination of anti-Toxoplasma antibody titers in the aqueous humor can be helpful. A comparison of serum levels of anti-Toxoplasma antibodies with the levels found in aqueous humor may identify intraocular production of antibodies, thus proving active ocular toxoplasmosis. This ratio, corrected for total protein concentration, is known as the coefficient of Witmer-Desmonts. When the coefficient of Witmer-Desmonts is less than 2 in an immunocompetent patient, there is no active ocular toxoplasmosis. If the ratio is between 2 and 4, it is suggestive of active ocular disease, and when the ratio is 4 or more it is considered diagnostic of ocular toxoplasmosis.

**COEFFICIENT OF WITMER-DESMONT S**

\[
\text{Titer of antibody in aqueous humor} \\
\times \frac{\text{Concentration of serum globulins}}{\text{Concentration of aqueous humor globulins}}
\]

Recently, PCR has become a powerful tool in making the diagnosis of ocular toxoplasmosis, especially if the serologic tests are equivocal. Aqueous or vitreous samples may be tested with high sensitivity and specificity for the presence of Toxoplasma DNA sequences using PCR.

**Treatment**

Indications for treatment:- Following are the main indications for treatment

1. Lesions threatening or involving the macula, papillomacular bundle, optic nerve head or a major blood vessel.
2. Lesions greater than 2DD in size associated with 3+ vitreous cells.
3. A very severe vitreitis causing marked visual impairment, which may subsequently lead to vitreous fibrosis and tractional retinal detachment.
4. Extensive chronic exudative lesions regardless of location
5. Loss of more than two lines in visual acuity
6. Persistence of inflammation for more than a month
7. Congenital Toxoplasma retinochoroiditis in the first year
8. Any lesion in an immunocompromised host

An ideal combination that destroys tissue cysts and hence prevents recurrence is yet to be found. Current therapies are targeted at destroying trophozoites. Drugs clinically used in the treatment of ocular toxoplasmosis include pyrimethamine, Sulphadiazine,Trimethoprim – sulphamethoxazole, Clindamycin and Azithromycin.

The following antibiotics can be used

1. Pyrimethamine - 100mg on first day, 75mg on second day, 50mg on third day followed by 25mg once daily and Sulphadiazine (4g daily divided 6th hourly) are given for 4-6 weeks.
2. Clindamycin - 300mg 6th hourly can also be given for 6 weeks
3. Trimethoprim+ Sulphamethoxazole DS (160/800mg) 1 BD for 6 weeks.
4. Azithromycin - loading dose 1 g first day followed by
500mg once a day for 3 weeks can also be given.

5. Atovaquone - 750mg 6th hourly for 4-6 weeks.

The use of pyrimethamine, sulfadiazine, clindamycin, folinic acid, and prednisone for vision-threatening ocular toxoplasmosis in the absence of contravening factors is a good option. The optimal duration of specific therapy has not been clearly defined. However it should be given for 30 to 60 days in an immunocompetent patient. A positive response to treatment is defined as a sharpening of the borders of the retinochoroidal lesions and improvement of vitreous haze. When therapy is complicated by adverse effects or proves to be ineffective after 4 months, a change in therapy is recommended. Steroids are added to minimize damage to other ocular structures caused by inflammatory response. Steroids alone should not be given without antibiotic coverage because retinitis represents active proliferation of toxoplasma organism. Steroids should be started 48 hrs after initiation of antibiotic and should be stopped prior to its discontinuation. Topical steroids and cycloplegics can be added to treat associated anterior uveitis.

When a pregnant woman acquires toxoplasmosis, spiramycin (500mg 6 hourly) in combination with pyrimethamine or sulfadiazine may be administered for a 3-week period. If the response is not adequate, the regimen can be repeated after 21 days. Prednisone can be introduced if needed.

The newborn with a diagnosis of congenital toxoplasmosis also requires special consideration. The suggested regimen is a combination of pyrimethamine, sulfadiazine, and folinic acid (5-20mg /day depending on neutrophil count).

### Anti - Toxoplasma therapy in special situations

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<td>2&lt;sup&gt;nd&lt;/sup&gt; Trimester – Spiramycin + Sulfadiazine + Pyrimethamine + Folinic acid</td>
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<td>3&lt;sup&gt;rd&lt;/sup&gt; Trimester – Spiramycin + Pyrimethamine + Folinic acid</td>
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| Newborn | Pyrimethamine, Sulfadiazine and Folinic acid |

### Surgical treatment

Photocoagulation and cryotherapy may not be of much use in active lesions because it can precipitate retinal and vitreous hemorrhage and even retinal detachment. Furthermore toxoplasma cysts may reside in ophthalmoscopically normal retina making either of these two treatments unlikely to be curative. Successful use of intravitreal clindamycin (1.0mg/0.1ml) for toxoplasma retinochoroiditis, in patients intolerant to or non responsive to systemic medications have been reported. Combination of intravitreal clindamycin (1.5 mg/0.1ml) and dexamethasone (400µg/0.1ml) injections 30 minutes apart (weekly injections till the lesions resolve) for treatment of zone -1 toxoplasma retinochoroiditis in patients nonresponsive to or intolerant to oral clindamycin and in pregnant ladies (injections every 4 weeks) is also reported. Toxoplasmic CNVM has been treated successfully with vertiporfin photodynamic therapy. Pars plana vitrectomy is performed to treat persistent vitreous opacities or vitreoretinal traction.

### Prognosis

The prognosis of ocular toxoplasmosis (that does not involve the optic nerve or the central macula) is favorable in most cases, because the active disease is self-limiting. In some cases, however, sequelae such as a macular retinochoroidal scar, severe vitreous haze, glaucoma, macular edema, epiretinal membrane, choroidal neovascularization, and retinal detachment may cause severe loss of vision. Factors that lead to a worse visual prognosis are large lesions, proximity to the fovea, and a long duration of disease.

### Prevention

Important measures to prevent infection include the following:-

1. Meat should be cooked to 60°C (140°F) for at least 15 minutes or frozen to temperatures below - 20°C for at least 24 hours to destroy the cysts.
2. Any contact with cat feces should be avoided.
3. Hands should be washed after touching uncooked meat and after contact with cats or soil that could be contaminated with cat feces.
4. Consumption of raw eggs and non pasteurized milk, particularly goat’s milk, should be avoided.
5. Fruits and vegetables should be adequately washed before ingestion.
6. Blood transfusions and organ transplants from seropositive donors should be avoided if the recipient is seronegative.
7. Adequate cooking of meat, avoidance of contact with...
infected pets and avoidance of drinking contaminated water.

**Conclusion**

Toxoplasmosis is a recurrent and progressively destructive ocular and systemic parasitic disease which is largely preventable with potentially blinding and fatal consequences. Early diagnosis and appropriate treatment are of utmost importance.

**References**

1. Ocular Toxoplasmosis: Jabs DA, Nguyen QD; in RETINA (vol II) 4th edition 1583-1595