RECENT ADVANCES IN THE MANAGEMENT OF OCULAR TOXOPLASMOSIS

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Toxoplasma gondii is an obligate intracellular parasite in which members of the cat family are the definite hosts. Oocysts in the cat intestine are released and spread in fecal material directly to human and or indirectly via the consumption of partially cooked meat prepared from other infected animals such as pigs, sheep and chicken. Cysts containing numerous tachyzoites may exist within the tissue without causing damage. However, degenerating cysts incite a marked inflammatory response, causing much tissue disruption (Langstone, 1985).

Toxoplasmosis is the most common proved cause of chorioretinitis in the world. It is almost always congenital but very rarely maybe acquired. It is an important cause of blindness and visual morbidity, affecting young adults and probably the most common cause of inflammatory disease of the posterior segment of the eye. Systemic toxoplasmosis is a benign disease unless the patient is pregnant or immunocompromised. Overall it accounts for about 7-15% of all uveitis and 8% of cases of posterior segment intraocular inflammation, in 1-2% of patients with AIDS in the USA and 8% in South America (Anonymous, 1998; Langstone, 1985; Schlaegel, 1985).

Congenital systemic toxoplasmosis may or may not be active at birth; the signs and symptoms are convulsions, scattered intracranial calcifications and retinochoroiditis. The latter is present in 80% of children with congenital toxoplasmosis and is bilateral in 85% of these with a predilection for the macular area. Although ocular toxoplasmosis may not make its first appearance until adulthood, most infections with *Toxoplasma gondii* are congenital in origin and have a predilection for the nerve fiber layer. Microphthalmos, posterior uveitis, optic atrophy, iritis, strabismus and nystagmus are the ocular signs most often associated with severe congenital toxoplasmosis and may be well developed at birth. Ophthalmoplegia and nystagmus are usually due to CNS involvement (Schlaegel, 1985).

All women getting married should have a serologic test for toxoplasmosis, if positive, they can be assured that they are immune and not able to pass toxoplasma to any of their children. If negative, they will need to be cautious during pregnancy to avoid infection of the fetus. If a pregnant woman acquires the disease, there is a 40% chance that her infant will be infected (Langstone, 1985).

In the Department of Obstetric and Gynecology Cipto Mangunkusumo Hospital the positive serological test for toxoplasma in pregnant women without the history of abortion was 46.6% and that with abortion was 64.8% and 53% of those women were associated with low immune status (Surjana, 2000).

Clinically in both the congenital and the acquired ocular disease, there is an acute focal chorioretinitis having its active onset of recurrence between ages 11 and 40 years old. Lesions may be single, variable in size, and are usually posterior to the equator. There is exudation into the vitreous and flare and cells in the anterior chamber. Vitreous may detach from the retina, with hemispheric collections of cells looking like keratic precipitates deposited on the back of the vitreous body and dubbed vitreous precipitates. The active disease often occurs next to an old scar to produce the so-called satellite lesion, it is usually one disc diameter in size, although it may vary from pinpoint to extremely large. Activity in the lesion persists for about 4 months. It is less frequent in blacks and most frequent in teenage girls. Papillitis and papilledema are not uncommon. A rare type of vitreous reaction with the development of grapevines in the vitreous covered with wet snow may be seen. If the macular area is not involved, and the inflammation is mild, the condition maybe asymptomatic. Activity of a lesion is manifested by its softness and elevation and by the presence of cells in the vitreous over it, although the latter may persist in the vitreous for months. Their presence, therefore, is not an absolute guide.

One of the complications of congenital chorioretinitis caused by toxoplasmosis is secondary divergent squint or exotropia. As the site of predilection of infection by *Toxoplasma gondii* is on the macular area of the fetal eye, this will lead to disturbance in the visual acuity as well as visual development, a severe obstacle to sensory fusion and may abolish the fusion mechanism altogether and produces strabismus.

In immunocompromised individual as AIDS, the

inflammatory reaction may be severe, multiple or bilateral, and in some cases the associated infection by cytomegalovirus (CMV retinitis) may aggravate the condition (McCluskey, 1994; Brew and Currie, 1994).

The commonest cause of focal cerebral lesions in patients with AIDS is toxoplasmic encephalitis, due to reactivation of past infection. Up to 47% of *Toxoplasma* seropositive individuals may develop encephalitis, manifests with subacute development of focal neurological deficits. A brain CT scan usually shows multiple bilateral ring enhancing cerebral lesions, space occupying lesions of *Toxoplasma gondii* abscesses, often at the cortico-medullary junction or basal ganglia, produces rapidly evolving signs of raised intracranial pressure including papilledema and sixth nerve palsies and fields defects. The definitive diagnosis requires the demonstration of tachyzoites histologically or by detection of specific toxoplasma DNA by PCR (McCluskey, 1994; Brew and Currie, 1994).

Pathogenesis

The etiology of the initial disease is the protozoan *Toxoplasma gondii*, but reaction of disease may be due to a number of mechanisms, including (1) local proliferation of free forms following rupture of a retinal cyst, (2) delayed hypersensitivity specific for *Toxoplasma* cyst content, (3) hypersensitivity to retinal proteins from tissue breakdown, (4) recurrent parasitemia, and (5) wandering cells that liberate *Toxoplasma* into ocular tissue, allowing invasion of susceptible cells.

The differential diagnosis of congenital toxoplasmosis includes macular coloboma, herpes simplex chorioretinitis, neonatal hemolysis, torulosis, cerebral trauma, and foci of retinoblastoma, in adults, tuberculosis, candidisis, and histoplasmosis need to be considered. Other causes of necrotizing retinochoroiditis should be considered especially in immunocompromised individuals such as herpes simplex, syphilis and atypical CMV retinitis. Acquired toxoplasmosis is characterized by fever, myalgia, and lymphadenopathy. In such rare cases a rising antibody titer is seen.

Diagnosis

Diagnosis is based on the characteristic clinical picture, and may be assisted by the following laboratory evidence and tests. The serologic tests must be run down to undiluted serum (1:1 titer). The indirect fluorescein antibody test and the hemagglutination test are now the two most commonly employed. The old Sabin-Feldman methylene blue dye test is obsolete. The chances of a test being positive in the population at large are roughly equal to the patient's age. A 50-year-old person has about a 50% chance of having a positive test; therefore, the test can be false positive, especially in older individuals. One must not look for a rising titer because most cases are due to congenital infection, so the antibody titer is low and remains there. In such congenital cases only one antibody titer is greater than 1:1,000.

The immunofluorescent antibody test has been superseded by the dye binding test and ELISA. Raised level of antibody IgG to *Toxoplasma* antigens indicate previous exposure to the organism and are present in many normal healthy individual. Raised IgM level or a rising titer of IgG antibody indicate a recent exposure to the organism but may not necessarily imply active intraocular infection. The presence of IgM antibody in the newborn indicates congenital infection. Raised aqueous or vitreous IgG level above the serum level (Goldmann-Wittmer coefficient greater than 3) indicate intraocular antibody production and suggest active infection. Importantly, negative serology excludes the diagnosis (Candolfi *et al*, 1987).

Detection of circulating antigens during reactivation of chronic toxoplasmosis in immunocompromised patients whose antibody response is inadequate, may suggest that the presence of circulating antigens indicate active infection and that determination of antigen in serum might be useful for early diagnosis of reactivated toxoplasmosis (Candolfi *et al*, 1987; Verhofstede *et al*, 1987; Suzuki *et al*, 1988; Weiss *et al*, 1987).

PCR

Screening during pregnancy to establish prenatal diagnosis of toxoplasma by PCR test performed on amniotic fluid is a rapid, safe and accurate (Hohlfeld *et al*, 1994). Detection of parasite-specific genes using appropriate primers and PCR technique on mRNA extracted from vitreous samples or in paraffin embedded material confirm intraocular infection. However a recent comparison of serological test to PCR-based tests indicates that serology is more reliable (Hohlfeld *et al*, 1994; Mohkya *et al*, 1999). Brain CT scan and magnetic resonance imaging (MRI) in patients with AIDS may reveal intracerebral lesions. These have a predilection for the basal ganglia, but may occur anywhere. Typically they appear as enhancing ring-like lesions of toxoplasma abscess surrounded by areas of brain edema (McCluskey, 1994; Brew and Currie, 1994).

Treatment and management

Indications of treatment depend on size, location and severity of the lesion and whether vision is

impaired. Small lesion at the periphery of the retina may be a symptomatic and passed unnoticed by the patient. Lesions encroaching on the macula or in the juxtapapillary area require treatment. Large lesion in the periphery causing extensive vitreal opacification or causing retinal complication such as serous detachment also requires treatment (Anonymous, 1988; Langstorn, 1985; Schlaegel, 1985; Smith, 1989).

Systemic corticosteroid should not be used alone without specific antimicrobials, as the patients' immunity is not strong enough to prevent the rampant multiplication of the parasite, resulting in serious damage (Anonymous, 1998; Schlaegel, 1985). Periocular injection of depomethylprednisolone acetate adjacent to the area of the lesion should be avoided, as this route of therapy may be immunosuppressive, resulting in an uncontrolled proliferation of the organism and disastrous clinical results (Anonymous, 1998).

Medical treatment is a combination of systemic corticosteroids and at least one antitoxoplasmic agent and preferably two or three, or even quadruples therapy. Standard 'triple' therapy is the mainstay of toxoplasmic retinochoroiditis drug therapy: Pyrimethamine 75-100 mg orally (loading dose) given over 24 hours, followed by 25 mg once or twice daily for 4-6 weeks depending on the clinical response. Sulfadiazine 4g loading dose followed by1.0-2.0 g, four times daily for 4-6 weeks. Prednisone 60-150 mg daily for 3 days, tapering to 20-40 mg daily for 2-6 weeks, depending on the clinical response. Steroids therapy should be tapered-off before pyrimethamine / sulfadiazine is stopped.

Pyrimethamine is used at levels of 100mg PO bid the first day and 25 mg PO bid for 6 weeks or until activity subsides. As pyrimethamine acts only on actively dividing *Toxoplasma*, only active cases are treated with this drug. To avoid toxic depression of the bone marrow, folinic acid (leucovorin, 3mg,) once or twice weekly counteracts development of thrombocytopenia without interfering with therapeutics. Leucovorin comes in an ampule that may be given by injection, but the patient may be taught to put it in any liquid except alcohol and take it orally. The patient should not take folic acid, which would counteract the effect of sulfa or pyrimethamine. Platelet count should be done once weekly if pyrimethamine is used. If it falls to below 100,000 pyrimethamine should be stopped but steroids not discontinued. Leucovorin, 3 mg IM daily, should be instituted until platelet count returns to normal.

Sulfadiazine (triple sulfa) is given as three 500-mg tablets PO q6h for 4-6 weeks along with pyrimethamine, clindamycin, or tetracycline. In pregnancy pyrimethamine should be avoided because or induced congenital malformation.

Other antitoxoplasmic agents include: tetracycline, clindamycin, and sulphamethoxazole. Tetracycline is used with a loading dose of 2,000 mg, followed by 250 mg, PO qid for 3-4 weeks. For bowel complications Lactinex is helpful. Clindamycin 300 mg per os qid may be used with sulfadiazine There is a danger of diarrhea and even death from this drug. Patients should be warned that if they have four bowel movements / day more than normal they should stop taking clindamycin. In about 1% of patients, severe pseudomembranous colitis develops. The concomitant use of triple sulfa acts to prevent this colitis. If clostridial colitis develops, it is best treated with oral vancomycin. Many ophthalmologists now use trimethoprim-sulfamethoxazole (160 mg / 800 mg) bid as an alternative to sulfadiazine with or without clindamycin and prednisone (Anonymous, 1998; Smith *et al*, 1989).

Newer agent for the treatment of toxoplasmosis is atovaquone, hydroxynaphthoquinone that has shown promise for the treatment of *Pneumocystis carinii* pneumonia in patients with AIDS acts by selective inhibition of mitochondria electron transport chain in protozoa also has significant *in vivo* and *in vitro* activity against *Toxoplasma gondii*. In animal models, atovaquone has activity against the encysted stage (bradyzoite) of toxoplasma infection. (Mepron, Burroughs Wellcome, 750mg tablets four times a day) Atovaquone is a cysticidal agent with the potential to eradicate even the encysted form of the parasite. This medication is highly fat soluble and is extremely well tolerated, even in systemically ill immunocompromised patients But further investigations is required before it is established as a front line treatment for ocular toxoplasmosis (Anonymous 1998; Pearson *et al*, 1999). Roxithromycin, an ether oxime derivative of erythromycin is also effective in acute infection of *T. gondii* in mice, but cannot demonstrate its activity *in vitro* (Luft, 1987).

In patients with AIDS, the commonest cause of focal cerebral lesions is toxoplasmic encephalitis due to reactivation of past infection. Up to 47% of *Toxoplasma* seropositive individuals may develop encephalitis, manifests with subacute development of focal neurological deficits (McCluskey, 1994; Brew and Cumie, 1994).

A CT brain scan usually shows multiple bilateral ring enhancing cerebral lesions, space occupying lesions of *T gondii* abscesses, often at the cortico-medullary junction or basal ganglia, produces rapidly evolving signs of raised intracranial pressure including

papilledema and sixth nerve palsies and fields defects. The definitive diagnosis requires the demonstration of tachyzoites histologically or by detection of specific toxoplasma DNA by PCR.

Fluorescein angiography is not of great help in following the progress of toxoplasmic retinochoroiditis.

Surgical treatment

In patients with strabismus where the retinochoroiditis scar is quiet, surgical correction could be indicated for cosmetic purposes only. But in children where the visual acuity of both eyes is still functioning well, surgery is indicated to help to develop the single binocular vision of the patient. Cryosurgery and photocoagulation are reserved for patients with persistent recurrences. Retinal neovascularization may be seen, and photocoagulation of neovascular lesion may prevent loss of vision secondary to vitreous hemorrhages. Par plana vitrectomy may be helpful when inflammatory membrane or floaters produce significant symptoms and perpetuate the inflammatory process (Anonymous, 1998).

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