Dissertation on

ROLE OF ORAL AZITHROMYCIN IN THE TREATMENT OF OCULAR TOXOPLASMOSIS

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CERTIFICATE

This is to certify that the dissertation entitled, **"ROLE OF ORAL AZITHROMYCIN IN THE TREATMENT OF OCULAR TOXOPLASMOSIS"** submitted by Dr.Richa Singh, in partial fulfillment for the award of the degree of Master of Surgery in Ophthalmology by the Tamilnadu Dr. M.G.R Medical University, Chennai is a bonafide record of work done by her in the Regional Institute of Ophthalmology,Government Ophthalmic Hospital, Egmore, Chennai, during the academic year 2008 – 2011.

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PART I

INTRODUCTION

Toxoplasmosis is the most common cause of posterior uveitis in the immunocompetent individuals. It is estimated that at least 500 million people worldwide are infected with this organism. In the developing world its prevalence is probably underestimated. Traditionally thought to be a self-limiting retinochoroiditis, ocular toxoplasmosis can cause sight threatening complications .In infants and in immunosuppressed individuals it can be associated with potentially fatal systemic toxoplasmosis.Earlier believed to be mostly a reactivation of infection acquired in utero, evidence shows that acquired infection is more common than previously thought. It is one of the few uveitides for which we can potentially make a definite diagnosis. The host – organism interrelationship has a influence on the disease manifestations. A variety of diagnostic and therapeutic measures are being researched to aid in managing the disease.

EPIDEMIOLOGY

An estimated half of the world's population is infected with toxoplasmosis. It is believed to affect at least 10% of the adults in the northern temperate countries and more than half the people in the mediterranean and the tropical nations. 20 -70% of the general population has a positive serology for the organism.

TOXOPLASMA GONDII- THE ORGANISM

It is an obligate intracellular parasite ,ubiquitous in nature ,being found all over the world.It belongs to phylum -Apicomplexa,class –Sporozoa and order – Eucoccidia. The definitive host of this organism are the members of the cat family and intermediate hosts are human beings, livestock and rodents.

The parasite is known to exist in three forms which include tachyzoite, bradyzoite and oocyst.

Tachyzoites are crescent shaped structures ,6-7 microns in length. They are the invasive form of the organism which multiply into daughter cells and result in the acute manifestations of the disease. They are disseminated throughout the body in the macrophages via lymph and blood and can penetrate virtually any nucleated cell. In the cell cytoplasm, the organism resides in a parasitiphorous vacuole which protects it.

Bradyzoites are the encysted form of parasite found within tissue cysts in structures like brain, heart and retina. It is found in vacuoles surrounded by cell membrane elaborated by the host, which protects it from

the host's immune reaction. When the cyst wall breaks down, bradyzoites develop into tachyzoites and lead to reactivation of infection.

Oocysts are oval in shape, 10-12 microns in length and found uniquely in the intestinal mucosa of cats. It is the product of sexual reproduction and shed in cat faeces. It can remain viable in soil for more than an year. Sporulation creates the infectious oocyst containing sporozoites which is ingested by cats and human beings where it multiplies in intestinal epithelial cells and produces tachyzoites.

Many of the antigens associated organism have been identified. SAG 1 or p30 is perhaps the most studied of the antigens and plays a role in the organism's ability to invade a cell. It is useful in the serological diagnosis of infection. SAG 2 or p22 is a cell surface antigen which can participate in antibody dependent, complement mediated lysis of tachyzoites. Another antigen is F3G3, antibody to which has been suggested to have the ability to confer passive immunity. These antigens could be used as a basis for vaccine development ,in that immunization against these antigens might abrogate rapid entry of tachyzoite into the cell.

LIFE CYCLE OF TOXOPLASMA

It can be divided into two stages, feline and non feline

Non feline – This is the stage the parasite spends in the intermediate hosts i.e human beings, mouse, sheep and pigs. These acquire infection by ingesting tissue cyst containing bradyzoite from raw or undercooked meat or the sporulated oocyst from ingesting contaminated soil. The cyst is digested by the acidic pH gastric secretion which releases bradyzoites or sporozoites. These enter the host's intestinal epithelium and transform into rapidly dividing tachyzoites. The tachyzoites attach to the host cell and form a parasitiphorous vacuole ,within which it divides. Finally ,the host cell ruptures, releasing parasites that infect the adjoining cells. Released tachyzoites can undergo two fates. They can be eliminated by the host's immune response by induction of parasitidal antibodies, activation of macrophages, interferon gamma production and stimulation of CD 8 lymhocytes. Some transform into tissue cysts containing bradyzoites which lodge into the CNS, muscles and the eye.

Feline – Cat ingests tissue cysts containing bradyzoites which undergo several intermediate stages and lead to the production of gametes. The gametes fuse with each other to form a zygote , which envelopes itself in a rigid wall and is secreted in the feces as an unsporulated oocyst. The oocyst

after 2-3 days of exposure to ambient temperature undergoes sporulation to form sporozoites. The sporulated oocysts may be ingested by the intermediate hosts and the lifecycle thus continues.

MODES OF TRANSMISSION OF INFECTION

Humans acquire the infection in a number of ways. Most often it is by eating the meat of infected animals containing the tissue cysts, particularly undercooked pork, and less commonly lamb, beef and chicken. Infection can also spread by coming in contact with contaminated cat faeces while handelling cat litter, consumption of unpasteurized goat milk, unwashed fruits and vegetables and inhalation of sporulated oocyst.

Congenital infection occurs due to transplacental spread of the organism. It is a feature of newly acquired infection in the mother and not of chronic infection. Primary maternal infection has been estimated to occur in 0.2-1% of pregnancies . The rate of congenital toxoplasmosis increases from 10-15% due to infection in the first trimester to 60% due to infection in the third trimester. Early trimester infection results in more severe infection with higher chances of spontaneous abortion.

OCULAR TOXOPLASMOSIS – PATHOGENESIS

The disease manifestations are controlled by the host's immune response to infection. The primary pathological finding is a coagulative retinal necrosis. Toxoplasma tachyzoites infect the retina causing an intense mononuclear inflammatory reaction in the retina and vitreous, whereas a granulomatous reaction usually occurs in the contiguous choroid. Vitritis and anterior uveitis may represent a hypersensitivity response.

Cysts on the other hand can persist for years in the tissue without inciting any response due to the presence of a host elaborated cell membrane. Nearly two third of the patients present with relapses. There are two main theories postulated to justify this .The first states that the dormant cysts rupture in times of immunosuppression or stress releasing T. gondii organisms which may either actively invade the retina or stimulate an inflammatory retinochoroiditis. The second theory states that it is an autoimmune response to the retinal antigens like the S- antigen that incites the retinochoroiditis.[28]

Humoral immunity can play a role in the lysis of organism when it is extracellular and antibody coated parasite may not form a protective membrane which is essential for its survival in the macrophage.

However it is the cell mediated immune response which is of prime importance in the host defense mechanism .Both CD4 and CD8 cells play a role. An autoimmune mechanism has been postulated too, wherein inflammation is initiated by the destruction of the retina by the parasite and subsequent sensitization to the uveitogenic antigen.

Host's Immune Response

The disease manifestation depends on the strain of Toxoplasma and the host's immune response. In evaluating 28 strains from around the world, Sibley and Boothroyd found that virulent strains had the same genotype while the non virulent strain were polymorphic, implying that specific strains were more likely to cause the disease.

The host's immune response is an important feature and determines the disease manifestations. When Toxoplasma organism passes through the digestive tract and finally enters the host cell , it does so at the gut mucosal level. This evokes the production of IgA antibody ,which is a modulator of protection and an indicator of infection. Also, titres of IgA against p30(SAG-1) are a useful marker of congenital and acute toxoplasmosis.

However, if the parasite evades the mucosal response, humoral and cell mediated immunity are activated. Humoral immunity induces the formation of IgM and IgG antibodies, which kill the parasite by various mechanisms, especially when extracellular.

Cell mediated immunity is the main protective response evoked by the parasite during infection. Antibody opsonized parasites are phagocytosed by macrophages, which leads to activation of macrophages. These kill the parasite by oxygen dependent and oxygen independent mechanisms. T cells activated by various parasite antigens lead to the production of various cytokines, the important ones being Interleukin -4(IL – 4) and Interferon gamma(IFN – gamma).These aid in the killing of the parasite.Also,CD4 and CD8 cells are cytolytic against parasite infected macrophages.

Immune Response In The Immunocompromised

Here, both cell as well as humoral mediated immunity is altered. Due to the decreased number of the helper T cells, there is no observed increase in antibody titres during exacerbation of infection. T-cells fail to secrete IFN- gamma and IL-2, which can result in persistence of infection.

CLASSIFICATION

Toxoplasmosis can be broadly classified into Congenital and Acquired forms.

CONGENITAL TOXOPLASMOSIS

It occurs due to transplacental spread of infection. If occurring in the first trimester , there is a 15-20% incidence of infection. Stillbirth, abortion and congenital anomalies are common. If occurring in the third trimester, there is a 40% incidence of infection which is often subclinical and less severe. Chronic maternal infection is not associated with congenital disease. More than 82% of congenitally infected individuals not treated as infants will develop retinal lesions by the time they reach adolescence.[29]

The most common manifestation of congenital toxoplasmosis is retinochoroiditis. Bilateral chorioretinal scars are seen in almost 80% of patients with congenital toxoplasmosis with a prediliction for the macula. This could be attributed to the theory of earlier vascularisation of the posterior pole than the periphery during development and the fact that fetal vasculature contains end arterioles. Another theory is that the parasite probably invades the eye through the Posterior Ciliary artery or the Optic nerve.[30] The retinal lesion tends to be self limited usually. Other ocular

manifestations include microcornea, microphthalmos, nystagmus and strabismus.

Acute congenital toxoplasmosis is a systemic disease with more serious implications. It is usually associated with low birth weight, fever, jaundice, maculopapular rash, pneumonia and hepatosplenomegaly. CNS involvement implies poor outcome and may result in microcephaly, hydrocephalus, seizures, disseminated intracranial calcification and psychomotor retardation. The classical triad of congenital toxoplasmosis consists of chorioretinitis, convulsions and intracranial calcification. Anti toxoplasma immunoglobulins (IgM) is present in 75% of infants with congenital toxoplasmosis.

ACQUIRED TOXOPLASMOSIS

It results commonly due to ingestion of tissue cysts from contaminated beef, lamb, pork or due to ingestion of oocysts from soil and vegetables. Rarely blood transfusions and accidental laboratory inoculation also result in infection. Usually subclinical and asymptomatic, about 10 – 20% of the cases can develop symptoms. These consist of fever, myalgia, lymphadenopathy and maculopapular rash sparing palms and soles. The disease is benign and self limited in immunocompetent individuals. Contrary

to the earlier belief that only 1-3% of these cases develop ocular manifestations, serologic studies reveal that ocular toxoplasmosis is more frequently associated with acquired disease. The retinochoroidal lesions are not associated with old scars in these cases.

CLINICAL FEATURES OF OCULAR TOXOPLASMOSIS

Patients usually present with unilateral reduction in visual acuity, floaters , metamorphopsia or may be asymptomatic. The classical clinical signs are as described below.

- **Anterior segment:** Either granulomatous or non granulomatous inflammation may be present. Therefore either fine or mutton fat keratic precipitates may be seen behind the cornea. Anterior chamber activity is detected in the form of cells and flare using a 1 x 1 mm slit beam. Sometimes there may be no evidence of AC activity. The grading system for cells and flare is given below.

Grading of AC cells : SUN 2005 Am J Ophthalmol 2005;140:509

Activity	Cells
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Grading of AC flare : SUN 2005 Am J Ophthalmol 2005;140:509

Grade	Description
0	none
1+	Faint
2+	Moderate(iris and lens clear)
3+	Marked(iris and lens hazy)
4+	Intense(fibrin or plastic aqueous)

- **Vitreous :** Usually severe vitritis especially overlying the lesion may be seen. Inflammatory cells may be see floating in the vitreous cavity and require a Hruby or a contact lens for visualization and grading. However vitreous haze is a better indicator of active inflammation than vitreous cells because it combines the optical effect of cellular infilteration and protein leakage. It can be graded with the help of a scale based on the view of the optic disc and posterior retina with the help of the indirect ophthalmoscope and a 20 diopter lens and comparison of the view with a standard photograph (Nussenblatt's method). This makes the system more reproducible than the other subjective grading systems.

- **Retina :** The organism's propensity to involve the neural tissue leads to a retinitis and secondary choroiditis. An area of active retinitis consisting of an oval or circular cream coloured lesion adjacent to an old atrophic chorioretinal scar is seen typically. There may be areas of haemorrhage in the region surrounding the active retinitis. Sheathing of blood vessels may be there.

3 morphological variants of the retinal lesion have been described

LARGE DESTRUCTIVE LESION	INNER PUNCTATE RETINAL LESION	OUTER PUNCTATE RETINAL LESION
Dense yellow white elevated lesion, >1 DD	Single/multiple areas of active retinitis associated with mild retinal oedema	Multiple gray white punctuate lesions at the level of RPE or deep retina
Associated with anterior uveitis and dense vitritis	Associated with mild vitreous reaction	Little or no vitreous reaction
Most common and serious variant		
Requires treatment irrespective of location	Requires treatment if present at macula	Resolves slowly and can recur in a satellite fashion

- Papillitis
- Rarely scleritis

The reasons for reduction in visual acuity in these cases are:

- Vitritis
- Lesions situated at the posterior pole with oedema and inflammation
- Lesions involving the macula

Complications associated due to ocular toxoplasmosis may be:

- Chronic iridocyclitis
- Cataract
- Retinal detachment
- Consecutive optic atrophy
- Choroidal neovascular membrane
- Branch retinal vein occlusion
- Secondary glaucomas
- Band keratopathy
- Cystoid macular oedema

Toxoplasmosis in the Immunocompromised

In the immunocompromised and elderly, ocular toxoplasmosis can be quite serious but more importantly, can be associated with fatal systemic infection. Toxoplasmosis may involve CNS, heart and lungs in patients who have undergone organ transplantation and in patients with lymphomas. In patients who have AIDS, ocular toxoplasmosis is less common than that of the CNS. The salient features of ocular toxoplasmosis in an AIDS patient are as follows:

- Usually the result of a newly acquired infection or disseminated infection unlike in an immunocompetent patient where it is mostly a reactivation of congenital infection.
- Extensive confluent areas of retinitis – usually greater than 5 DD.
- Bilateral disease -18-38% of the cases
- Solitary ,multifocal or miliary pattern
- Lower degree of vitritis than in an immunocompetent patient.
- Pre existing scars may be absent ,therefore diagnosis may be difficult.

- Usually progressive unlike in an immunocompetent patient, therefore a prompt diagnosis is necessary.
- Patient may have associated cerebral or disseminated toxoplasmosis, therefore a thorough evaluation is necessary.
- Ig M titres may not be detectable and Ig G may not rise. Therefore diagnosis can be confusing.

DIFFERENTIAL DIAGNOSIS –OCULAR TOXOPLASMOSIS

- Acute Retinal Necrosis
- Pars planitis
- Sarcoidosis
- Endogenous bacterial or fungal infection
- Syphilis
- Tubercular chorioretinitis
- Intraocular lymphoma

INVESTIGATIONS

- **SEROLOGY**

The diagnosis of ocular toxoplasmosis is always based on a compatible fundus lesion and supported by a positive serology for antibodies.

The significance of each type of antibodies are as follows:

- IgG – It appears after 2 weeks, peaks at 2 months and then persists in low titres throughout the life of the individual.
- IgM – It appears transiently within two weeks of infection and then disappears.
- IgA – It persists only for seven months.

The diagnosis of the disease by serologic means alone is not yet feasible, as emphasized by a study performed by Rothova and coworkers. They noted that even though IgG antibody positivity was seen in 100% of their patients with clinically apparent toxoplasmosis,58% of the control subjects also showed positive results. Phaik and coworkers estimate that at

least 77% of those with ocular toxoplasmosis had serotitres equal to or greater than 1:256,somewhat higher than those found in control subjects. Antibody titres do not correlate with ocular disease .Antitoxoplasma antibodies may be in very low titres and preferably should be tested in undiluted titres(1:1).

Nonetheless most believe that the diagnosis is very much a clinical one, with serologic findings being supportive but not definitive.

The serological tests for toxoplasmosis are classified as follows:

- Sabin Feldman test
- Indirect fluorescent antibody test
- Indirect haemagglutination test
- Complement fixation test
- ELISA

Sabin Feldman test : It is the gold standard and reference test for ocular toxoplasmosis.It is both highly sensitive and specific. Here live toxoplasma organisms are taken and mixed with test serum and complement. Serial dilutions are made and the titre at which more than 50% organisms are

unstained is considered. A titre of 1:4 is considered positive. This test does not correlate with the severity of the disease.

Indirect fluorescent antibody test : Here killed tachyzoites are mixed with patient's serum and fluorescein tagged antihuman serum against IgG or IgM.A titre of 1:8 is considered positive.It is useful in cases of acute and congenital disease.ANA and RF positivity may give false positive results.

Indirect haemagglutination test : It involves coating of lysed organisms onto red blood cells which are then exposed to the patient's serum;positive sera cause the RBC's to agglutinate. This becomes positive 2-4 weeks after infection and is more useful for screening purposes.

Complement fixation test : In this test a titre of 1:4 is considered positive and a titre of >1:32 indicates recent infection.

ELISA : This involves binding of the patient's antibodies to an excess of solid phase antigen. The complex is then incubated with an enzyme linked second antibody. Assessment of the enzyme activity provides measurement of the specific antibody concentration. This is a sensitive test used to detect IgG and IgM antibodies and can also be used to detect antibodies in the aqueous which are more specific than those of the serum.

- **PCR**

In individuals in whom toxoplasmosis is considered a diagnostic possibility but the presentation is atypical, Polymerase chain reaction of the organism's DNA is a useful diagnostic aid.[17] This can be done from ocular tissue sections or the aqueous humor.

Witmer Goldmann coefficient – This is the ratio of antibodies against Toxoplasma in the aqueous to that in the serum.It can be used to evaluate the intraocular antibody production.

- **IMAGING STUDIES**

FFA: Fundus fluorescein angiography shows hypofluorescence in the early phase followed by progressive hyperfluorescence secondary to leakage.

ICG: Indocyanine green angiography of active lesions are mostly hypofluorescent.Images not picked up by clinical examination or FFA are sometimes seen with ICG.

OCT: Optical Coherence Tomography is helpful in identifying potential complications, including epiretinal membrane, cystoids macular edema, vitreoretinal traction bands and choroidal neovascularization. Active lesions are depicted by a highly reflective intraretinal area corresponding to the area of retinitis and which also shadows the underlying choroid. The posterior hyaloid is thickened and detached over the lesion.[8]

USG B-Scan: It is indicated in the prescence of ocular media opacities especially in the vitreous.The most common findings include intravitreal punctiform echoes, thickening of the posterior hyaloid, partial or total posterior vitreous detachment and focal retinochoroidal thickening.

TREATMENT

Toxoplasma retinochoroiditis in an immunocompetent individual is often a self limited process. Therefore not every case of ocular toxoplasmosis requires treatment. The potential benefits of treatment need to be weighed against the risks associated with antimicrobial therapy.The inability of most of the current drugs to eliminate cysts and prevent recurrences should be kept in mind too.

Treatment is always warranted in case of congenital toxoplasmosis and in the immunocompromised. In case of toxoplasmosis in the immunocompetent ,opinion varies amongst practitioners. In 1991 Engstorm and associates conducted a survey of all physician members of the American Uveitis Society to determine the current practices in the management of ocular toxoplasmosis. Among the respondents only 5% treated all active lesions regardless of ocular findings. Majority agreed to treat in case of.

- Decreased visual acuity
- Macular or peripapillary lesions
- Lesions >1DD in size

- Lesions associated with moderate to severe vitritis
- Presence of multiple active lesions
- Persistence of active lesions for more than 1 month
- Any ocular lesion associated with recently acquired infection

The aims of treatment are

- To decrease the duration and severity of acute inflammation
- To lessen the risk of permanent visual loss by decreasing the size of the eventual chorioretinal scar
- To reduce the risk of recurrences

There are a variety of drugs used in the treatment of ocular toxoplasmosis. Each of these is discussed briefly below.

- **Pyrimethamine** – It belongs to the diaminopyramidine group.A potent inhibitor of dihydrofolate reductase ,it thereby inhibits folic acid metabolism. Human beings can utilize exogenous folinic acid for their cells ,unlike T.gondi. It is given as 75 mg PO loading dose followed by *Dosage* - 25 mg PO b.d dose. It has been shown to limit the size of the retinochoroidal scar in patients with toxoplasmosis.[19]

Interactions– Concurrent use with other antifolate agents like Methotrexate may result in bone marrow suppression.It should be discontinued if signs of folate deficiency develop.

Contraindications – Documented hypersensitivity, Megaloblastic anemia resulting from folate deficiency.

Precautions – Dose to be reduced or discontinued if signs of folate deficiency develop, depending on the patients response. Caution to be exercised in case of hepatic or renal impairment. May precipitate hemolytic anemia in a case with G-6-PD deficiency, especially under stressful conditions. In pregnancy fetal risk revealed in animal studies, but not established in humans. May be used if benefits outweigh the fetal risk.

- **Sulfadiazine** – Member of sulfa group of drugs. Exerts bacteriostatic action through competitive antagonism of PABA(para amino benzoic acid) and therby hampers folate metabolism.

  Dosage – 2 g p.o o.d loading dose followed by 1 g q.i.d

  Interactions – Increases the effect of oral anticoagulants and oral hypoglycemic agents. Effects of Sulfadiazine are decreased when administered along with PABA or PABA metabolites eg.Procaine, Proparacaine and Tetracaine.

Contraindication – Documented hypersensitivity

Precautions – Adverse effects include skin rash and renal crystallization, which can be avoided by a large intake of fluids. Treatment should be stopped if hematuria, albuminuria or crystalluria develops. Caution in impaired renal, hepatic function and in G-6-PD deficiency. Fetal risks revealed in animals but not documented.

- **Trimethoprim and Sulfamethoxazole** – Exerts bacteriostatic action through competitive antagonism with PABA.Regular strength tablets contain 80 mg Trimethoprim and 400 mg Sulfamethoxazole while double strength contains 160 mg and 800 mg of each respectively.

  Dosage -960 mg B.d

  Interactions – Coadministration with Warfarin may increase PT,with diuretics increases the incidence of thrombocytopenic purpura in the elderly, potentiates bone marrow depression with Methotrexate and hypoglycemic response with Sulfonylureas.

  Contraindications – Documented hypersensitivity, Megaloblastic anemia secondary to folate deficiency and during breastfeeding.

  Precautions – Discontinue at the first appearance of skin rash or significant hematologic changes occur. Goitre, dieresis and hypoglycemia may occur with Sulfonamides. Prolonged high doses may cause bone

marrow suppression which should be treated with 5-15 mg/d of Inj. Leucovorin. Caution to be exercised in patients with folate deficiency, with G-6-PD deficiency and in patients with AIDS, renal or hepatic impairment.

- **Clindamycin** – Belongs to the macrolide group and inhibits bacterial growth possibly by blocking the dissociation of peptidyl-t RNA from ribosomes, thereby arresting protein synthesis. Some animal evidence exists to show that Clindamycin helps in the eradication of the encysted form.

  Dosage – 300 mg p.o q.i.d

  Interactions – Increases the duration of neuromuscular blockade by Tubocurare and Pancuronium. Effects antagonized by Erythromycin and absorption delayed with concomitant antidiarrhoeal administration.

  Precautions – Can possibly cause severe colitis due overgrowth of Clostridium difficile. Caution in hepatic impairment.

- **Atovaquone** – It is a hydroxylnapthaquinine that inhibits the mitochondrial electron transport chain by competing with ubiquinone at the ubiquinone – cytochrome- reductase region (complex III). The inhibition of electron transport by Atovaquone will result in the inhibition

of nucleic acid ATP synthesis in the parasite. It has also shown activity against bradyzoites in the animal models of toxoplasmosis.

Dosage – It can be given as 750 mg qid PO.

Interactions – It may increase the serum levels of Zidovudine. Coadministration with Rifampicin may result in decreased levels of Atovaquone. It may decrease the serum levels of TMP-SMZ.

Contraindications – Documented hypersensitivity.

Precautions – Caution to be exercised in elderly patients and in those with hepatic and renal impairment.

- **Spiramycin -** Macrolide antibiotic, thought available for quite a long time, has been used only sporadically. Resembles erythromycin in properties and spectrum of action.

  Distinctly has been found to limit risk of transplacental transmission of Toxoplasma infection.

  Use – specific utility for toxoplasmosis and recurrent abortions in pregnant women.

  Dose – 3 week courses of 3 MU tid repeated after 2 weeks gap till delivery.

  Side effects – Gastric irritation, nausea, diarrhoea, rashes

DRUG	GROUP MECHANISM OF ACTION	DOSAGE	SIDE EFFECTS
PYRIMETHAMINE	Diaminopyramidine -Inhibits folic acid metabolism	75 mg o.d(LD) 25 mg b.d(MD)	Bonemarrow suppression GI intolerance
SULFADIAZINE	Sulpha group -Inhibits folic acid metabolism	2 g o.d(LD) 1 g q.i.d (MD)	Skin rashes Renal crystallisation
CLINDAMYCIN	Macrolide -Inhibits peptide chain elongation	300 mg q.i.d	Pseudomembranous colitis
COTRIMOXAZOLE	Trimethoprim and Sulfamethoxazole	960 mg b.d	Skin rashes Crystalluria
SPIRAMYCIN	Macrolide	400 mg t.i.d	Gastric irritation
MINOCYCLINE	Semisynthetic Tetracycline -Inhibits 30s ribosome during protein synhesis	100 mg b.d	Phototoxicity
AZITHROMYCIN	Macrolide	500 mg b.d	Gastric irritation
ATOVAQUONE	Antimalarial	750 mg q.i.d	Rashes GI upset

COTICOSTEROIDS

Corticosteroids have a role to play in the treatment of ocular toxoplasmosis.

Topical steroids may be used to curtail anterior chamber inflammatory reaction. Oral steroids are used to treat the inflammation associated with vitritis, vasculitis and macular edema. Since increased ocular inflammation and retinal necrosis may be seen in patients receiving oral steroids without antimicrobial therapy, it is recommended to start the latter at least 24 hours before the former .

Oral steroids should be tapered before discontinuing the antimicrobial treatment. In immunocompetent individuals treatment is continued till there is significant decrease in inflammation active. This is typically in the range of 4-6 weeks but occasionally may be longer. Depot steroid therapy is absolutely contraindicated in the treatment of ocular toxoplasmosis. The high dose medication in close proximity to the ocular tissues apparently overwhelms the host's immune response, leading to rampant retinal necrosis and potential for a blind ,phthisical globe.

CYCLOPLEGICS

These have a role to play in case of anterior uveitis. They help by

- Reducing ciliary spasm and the pain associated with it.
- Breaking the formed posterior synechiae.
- Preventing the formation of posterior synechiae further. Examples include 1%Atropine eyedrops or ointment, 2% Homoatropine eyedrops and 0.5% , 1% Cyclopentolate.

Precautions – Caution to be maintained in patients with a raised intraocular pressure. It can also cause toxic systemic anticholinergic effects when used in children, especially in infants. Compressing the lacrimal sac digitally for 1-3 mins after instillation may minimize systemic absorption.

There are 2 standard regimes for the treatment of ocular toxoplasmosis. These are the triple and the quadruple regimes. The former consists of Pyrimethamine in conjunction with Sulfadiazine and oral corticosteroids while the latter includes Clindamycin additionally. Folinic acid is administered concurrently with Pyrimethamine to prevent bone marrow suppression. A baseline blood count should be obtained before initiating treatment followed by weekly measurements to monitor for drug toxicity. Therapy should be discontinued if the WBC count falls below

4000/cc, platelet count below 100,000/cc or if either decreases 25-50% below the baseline. Rothova and associates found a relationship between treatment with Pyrimethamine and Sulfadiazine and reduction of lesion size. The search for better and less toxic antparasitic drugs has yielded 2 serious candidates, Atovaquone and Azithromycin both of which have exhibited in vitro and in vivo efficacy not only against tachyzoites but also against cystic forms of Toxoplasma[25]

During pregnancy Spiramycin is thought to be a safe drug and may reduce the rate of Toxoplasma transmission to the fetus. Other alternative drugs that have been used are Sulfadiazine and Pyrimethamine, but they are associated with several side effects and are best avoided.In a study carried out on Callomys callosus sp. of mice Azithromycin was shown to prevent the occurrence of congenital toxoplasmosis, but this remains to be proven in human beings.[15]

In the immunocompromised because of progressive nature of ocular disease treatment is recommended when there is active disease. The possibility of bone marrow suppression with pyrimethamine and corticosteroids are of concern. Long term maintenance therapy with clindamycin needed to prevent recurrence.

Genotypic strains of Toxopasma gondii and resistance to medication were recently suspected. Despite the fact that all lineages can infect human beings, type II strains are predominant in Europe and North America, type III strain and recombinant type I/III are more common in South America. Type I is highly virulent, type III strains of the intermediate type and typeI/II are nonvirulent. A recent paper of Pascale Meneceur et al has shown no significant difference in response of type I/II/III towards Pyrimethamine, Sulfadiazine and Atovaquone therapy.

SURGICAL TREATMENT

Surgical treatment including photocoagulation, cryotherapy and vitrectomy has been tried, but efficacy not clearly demonstrated. The potential for retinal or vitreous hemorrhage and even retinal detachment when treating an acutely inflamed retina makes surgical intervention less desirable in active disease. Also, given that normal appearing retina can harbor Toxoplasma cysts, the above procedures cannot predictably prevent disease recurrence.

Pars plana vitrectomy may be indicated in cases of retinal detachment secondary to vitreous tractions or when vitreous opacities are present.

However treatment with antimicrobial agents is indicated before and after surgery.

Role Of Azithromycin

It belongs to the macrolide group which also includes Erythromycin and Clarithromycin. Its structure consists of a large lactone ring to which sugars are attached.

Dosage – Max adult dose – 2000 mg/day

Max pediatric dose – 20-30 mg/kg/day

Mechanism of action – It binds specifically to 50s subunit of ribosome thus inhibits peptide chain elongation, and thereby inhibits bacterial protein synthesis.

Pharmacokinetics – The remarkable properties of Azithromycin are acid stability, rapid oral absorption, marked tissue distribution and intracellular penetration. Particularly high concentrations are obtained inside macrophages and fibroblasts. It is largely excreted unchanged in bile, renal excretion is less than 10%.

Spectrum of action – It is similar to the other macrolides, but is less active against gram positive cocci and more active against H.influenzae. It is

highly active against Legionella, Mycoplasma, Campylobacter, Chlamydia and Moraxella.

Growing evidence of data suggests that the drug Azithromycin also has anti inflammatory activity through inhibition of transcription factor NF – Kb. The anti inflammatory potency is about 4 times weaker than hydrocortisone and 14 times weaker than dexamethasone.[31]

Uses of Azithromycin –

It is the drug of choice in Legionnaire's pneumonia and infections due to Chlamydia trachomitis. Other indications are pharyngitis, tonsillitis, otitis media, pneumonias, Streptococcal and some Staphylococcal skin infections. Malaria and toxoplasmosis are also its potential indications.

Drug interactions – Azithromycin has been found not to interact with hepatic CYP3A4 enzyme. Interaction with terfenadine, warfarin, carbamazepine and theophylline is not likely, but not totally ruled out.

Adverse reactions – Serious adverse effects are rare. Most of the side effects are gastrointestinal and include nausea, vomiting and diarrhea. These can occur equally for oral as well as intravenous formulations.

In ocular toxoplasmosis , its action is perhaps inhibition of protein synthesis .In vitro and in vivo efficacy against toxoplasma gondii has been reported,with an effect on the cystic form if administered for longer than 4 weeks[20]. Also Atovaquone and Azithromycin have been shown to reduce tissue cysts in animal models.[24] Furthurmore, it penetrates readily into the brain tissue.[22]However the concentration of Azithromycin in the ocular tissue is not yet known.

Its efficacy can be attributed to it readily crossing the blood brain and blood ocular barrier being widely distributed in tissues. It can be considered in patients who cannot tolerate the side effects of the conventional anti toxoplasma medications.

In AIDS patients, the standard regime results in the regression of the disease activity, but is associated with severe complications. Approximately, 40% of the immunocompromised and about 26% of the immunocompetent individuals discontinue treatment due to drug toxicity[25]. Azithromycin, when given for protection against disseminated M.avium complex infection in AIDS patients, was well tolerated [25]. It can be therefore assumed that it will be well tolerated by these patients even when they have advanced disease.

PREVENTION OF INFECTION

- Meat to be cooked to 60 degrees for at least 15 mins or frozen to temperatures below – 20 degrees for at least 24 hours to destroy the cysts.
- Any contact with cat feces to be avoided.
- Hands to be washed after contact with uncooked meat and after contact with cats or soil that could be contaminated with cat feces.
- Consumption of raw eggs and unpasteurized milk, especially goat's milk to be avoided.
- Fruits and vegetables to be adequately washed before ingestion.
- Daily cleaning of cat litter box removes the oocysts before they become infectious, because they need 1-3 days after excretion to undergo sporulation. This duty should be only performed by a non pregnant individual.
- Blood transfusions and organ transplants from seropositive donors to be avoided if the recipient is seronegative.

PART II

AIM OF THE STUDY

1. To study the effect of oral Azithromycin on the lesions of ocular toxoplasmosis on 50 patients with respect to

- Reduction in vitreous haze
- Change in the morphology of the retinal lesion
- Appearance of any new lesions

2. To compare the characteristics, namely lesion size and its associated vitreous haze, of lesions which heal by 6 weeks with those which do not heal by 9 weeks.

INCLUSION CRITERIA

1. Patients with fundal lesions clinically suggestive of ocular toxoplasmosis i.e presence of vitreous cells and vitreous haze along with active retinochoroiditis lesion with or without an adjacent old scar.

2. Lesions present with the following characterstics:
   - Location at or around the optic disc, macula, papillomacular bundle, at/near the vascular arcades or
   - Associated with vasculitis or haemorrhage or
   - Lesions presenting with moderate to severe vitritis or
   - Multiple lesions
3. Patients with a positive serology for antitoxoplasma antibodies (IgM or IgG).
4. Immunocompetent patients

EXCLUSION CRITERIA

1. Immunocompromised patients
2. Patients with an active choroiditis lesion but a serology negative for toxoplasma infection.
3. Retinal lesions at locations apart from the abovementioned.
4. Grade 4 vitreous haze
5. Patients with other causes of for reduced vision.
6. History of glaucoma or ocular hypertension.
7. Uncontrolled diabetes mellitus or hypertension.
8. Severe systemic disease.
9. Known hypersensitivity to Azithromycin.

10.

MATERIALS AND METHODS

This was a prospective study carried out between March 2009 and Sept 2010 in the department of Uvea services at RIOGOH,Chennai.

A detailed clinical history was taken from each patient ,the salient points of which were

- Clinical symptoms including reduction in visual acuity
- History of floaters
- Pain ,redness and photophobia
- Any history of fever,rashes,joint pains,ulcers
- Any of major systemic disorders like Tuberculosis,Diabetes and Hypertension
- History of consumption of undercooked meat or contact with pet animals.
- History of unprotected sexual exposure.
- Known allergy to any drugs ,especially Azithromycin

The patients were then subjected to a detailed clinical examination,both ocular and systemic. Anterior segment examination was done using slit lamp biomicroscopy. Posterior segment examination was done using 90 D lens and binocular Indirect ophthalmoscope and fundus drawing was done.

The following parameters were recorded:

- Baseline visual acuity and IOP
- Baseline vitreous haze,retinal lesion location,size and morphology.

The patients were then subjected to the following investigations:

- Complete blood count
- Erythrocytic sedimentation rate
- Mantoux, Chest X-ray
- VDRL
- ELISA for HIV 1 and 2
- TORCH profile
- RBS

Patients who were suspected to have toxoplasmosis clinically and based on serology were started on antimicrobial therapy.

Guidelines for treatment

- The patients were started on Tab. Azithromycin 500 mg b.d for a period of 3 weeks .
- Oral corticosteroids - Tab Prednisolone 1mg/kg body weight o.d, along with Tab. Ranitidine 150 mg b.d was started 2 days after starting Azithromycin.It was gradually tapered while finishing the course of Azithromycin.
- In the prescence of anterior uveitis treatment with cycloplegics -2% Homotropine b.d and topical corticosteroids –Prednisolone acetate eyedrops 6t/day was started and subsequently tapered.

Guidelines for follow up

Patients were required to visit the clinic once a week for a period of 3 weeks. Thereafter they were supposed to follow up at 6 weeks, 9 weeks and at 6 months.The results published are for a period of 6 months of follow up.

Main outcome measures

- Grading of vitreous haze.
- Retinal lesion size and morphology.
- Any new retinal lesions.

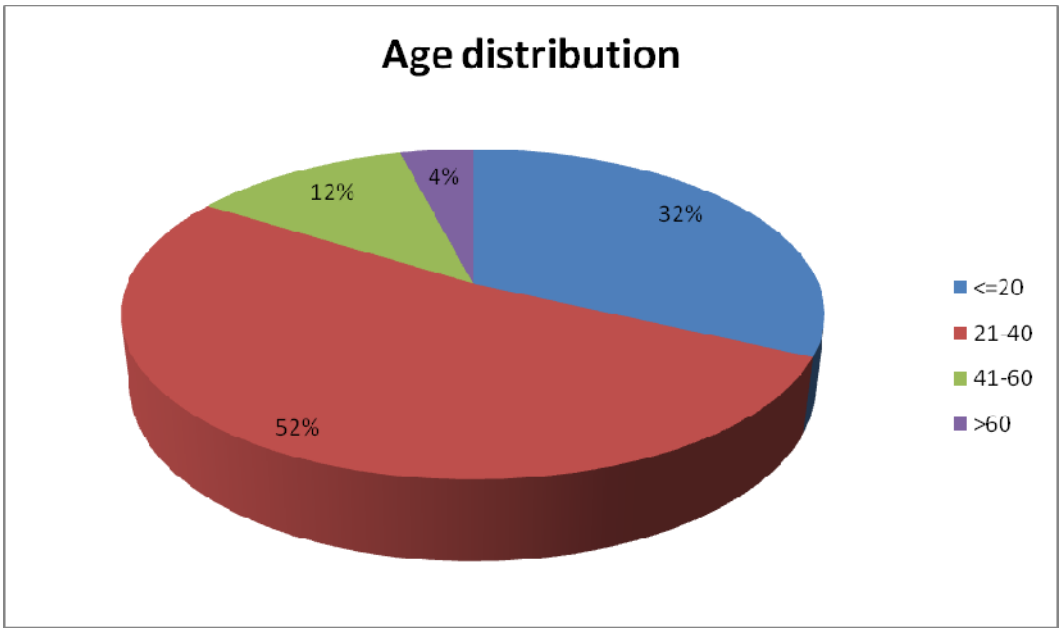
Best corrected visual acuiy(BCVA) by Snellen chart was recorded. The treatment with Azithromycin was considered successful if there was absence of intraocular inflammation, if the retinal lesion became flat and well demarcated at 6 weeks ,which is the time normally taken for the drug's effect to manifest. Since the disease is mostly self limiting in immunocompetent individuals and normally resolves by 10 weeks , lesions which resolved by this time were not included as therapeutic success of the drug.

OBSERVATION AND RESULTS

Age distribution

Total no. of patients – 50

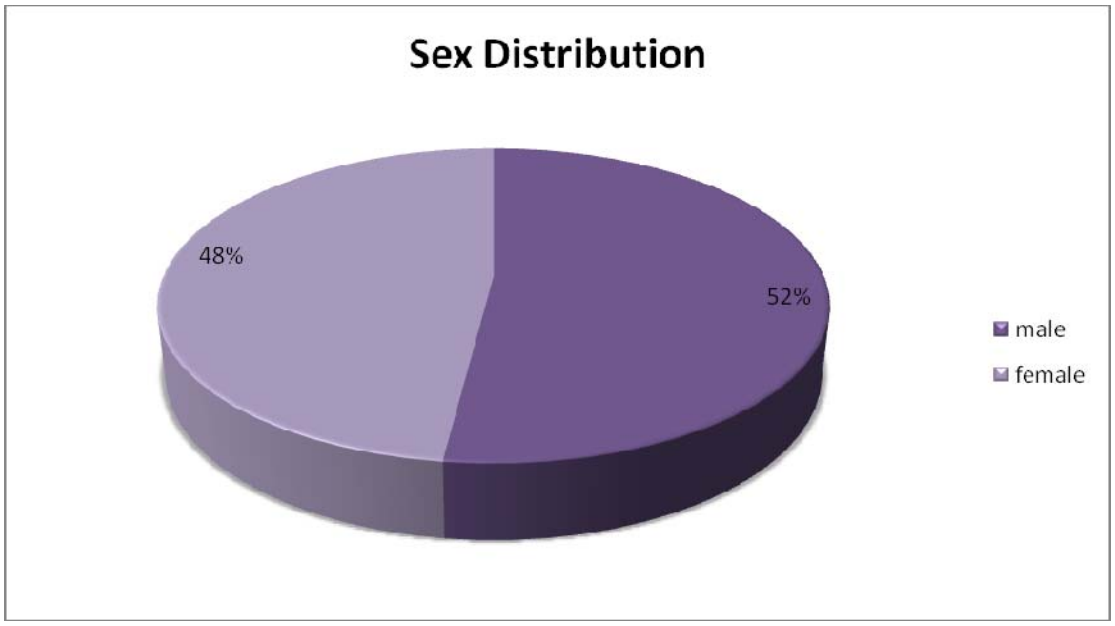
Age distribution	No. of patients	percentage
<=20	15	30
21 - 40	26	52
41 - 60	7	14
>60	2	4



Most of the patients in the study were in the age group 21 -40 years followed by the group < 20 years and then 41 -60 years.

Sex distribution

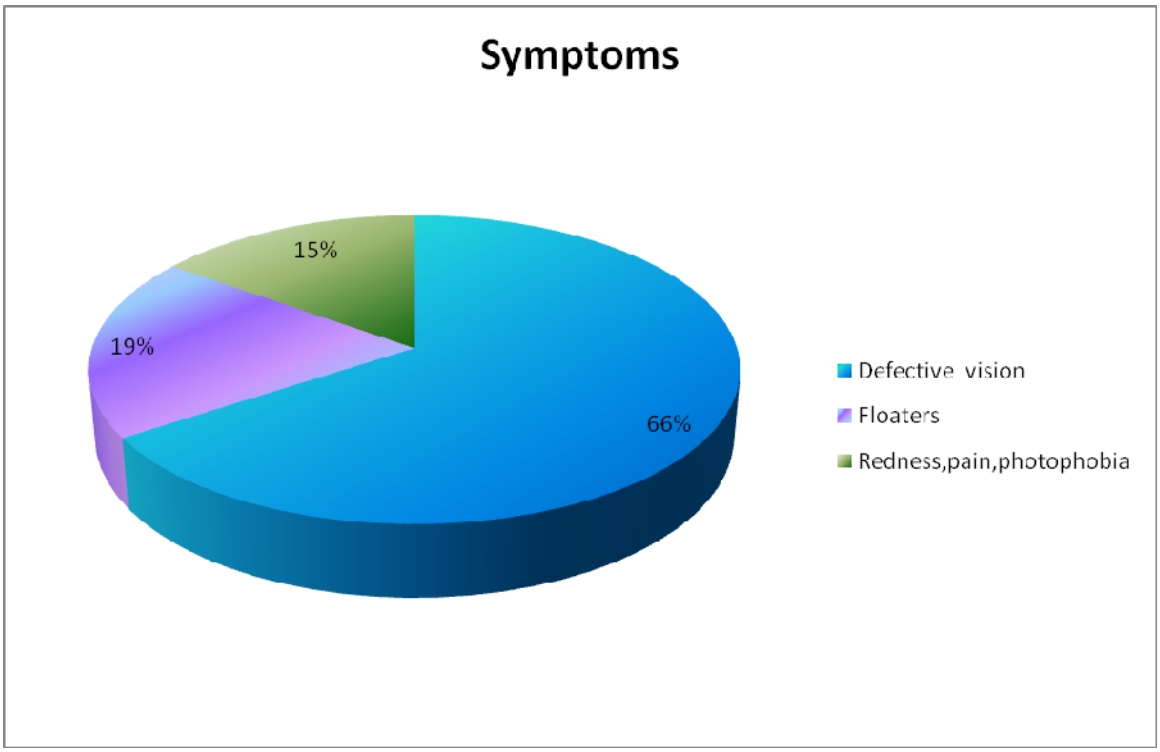
Sex	No. of patients	percentage
Male	26	52
Female	24	48



The sex distribution of the patients was almost equal with males exceeding the females by a marginal 2%.

CHIEF OCULAR SYMPTOMS

Symptom	No. of patients
Defective vision	48
Floaters	19
Redness, Pain, Photophobia	11



The majority of the patients (66%) complained of defective vision as their chief complaint. Floaters were the second most common symptom in (19%) of the patients. Pain, redness and photophobia was present in 15%.These symptoms were not exclusive and many patients presented with more than one symptom.

ANTERIOR SEGMENT INVOLVEMENT

Present	Absent
15	35

The majority of patients i.e 70% did not have any involvement of the anterior segment.

DISTRIBUTION OF VITREOUS HAZE

Total no. of patients - 50

Grading of vitreous haze	No. of patients
1	15
2	23
3	12
4	0

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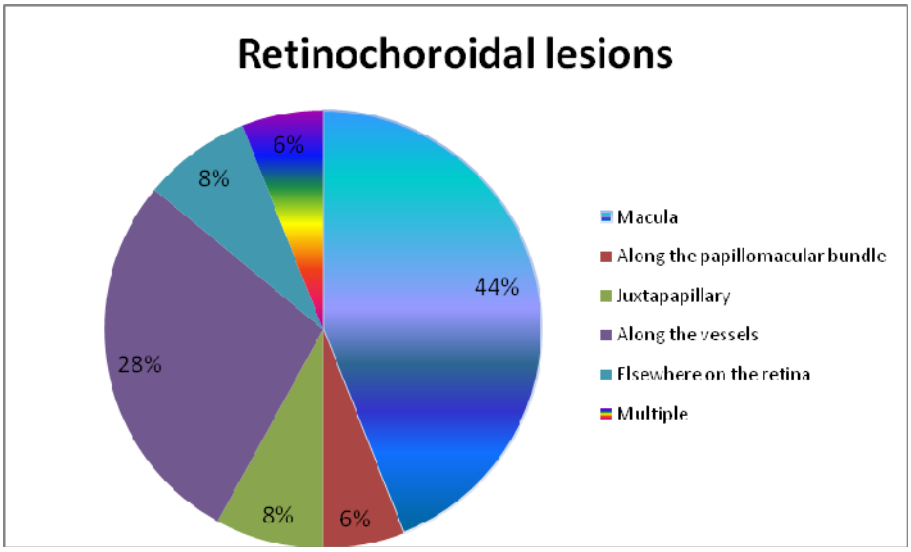
Most of the patients (46%) presented with a vitreous haze of Grade 2 ,followed by Grade 1 (30%) and Grade 3 (24%). Measurement of the vitrous haze was done by the comparison chart method of Nussenblatt.

LOCATION OF THE RETINOCHOROIDAL LESION

Total no. of eyes studied – 100

Lesion location	**No. of eyes affected**
Macula	22
Along the papillomacular bundle	3
Juxtapapillary	4
Along the vessels	14
Elsewhere on the retina	4
Multiple	3



Most of the retinochoroidal lesions in this study were located at the macula (44%) and along the blood vessels (28%).This was followed by lesions at juxtapapillary region and lesions elsewhere on the retina which were associated with significant vitreous haze.

RESULTS OF TREATMENT WITH ORAL AZITHROMYCIN

PRE – TREATMENT VITREOUS HAZE

Vitreous haze grading	No. of people	Percentage
1	15	30
2	23	46
3	12	24

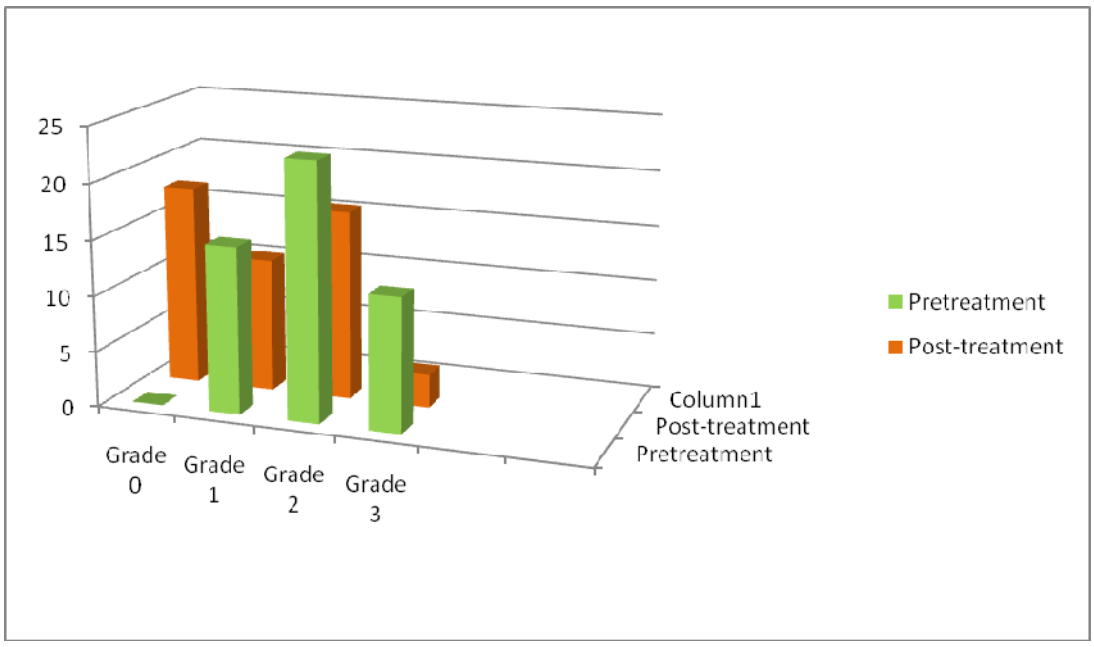
POST-TREATMENT VITREOUS HAZE

Vitreous haze grading	No. of people	Percentage
0	18	36
1	12	24

2	17	34
3	3	6

COMPARISON BETWEEN PRE AND POST TREATMENT

VITREOUS HAZE



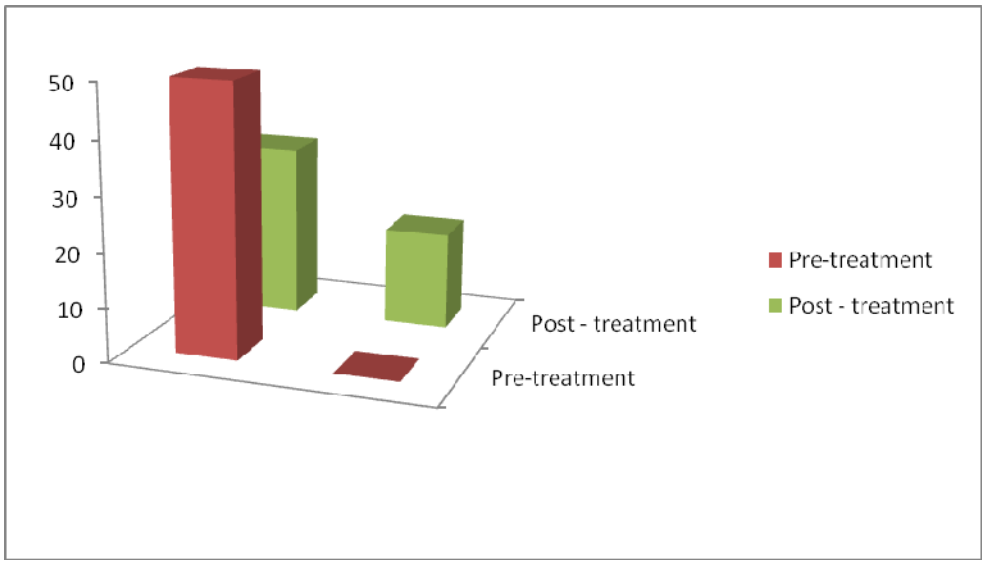
There was a definite reduction in vitreous haze in most of the patients.Maximum reduction was seen in the number of people having grade

3 haze,reducing from 24% to 6% at 6 weeks.36% of the patients had no vitreous haze at 6 weeks.

LESION MORPHOLOGY AT 6 WEEKS

	Active lesions	**Inactive lesions**
No. of people	32	18
Percentage	64	36

COMPARISON OF LESION MORPHOLOGY AT 6 WEEKS



Out of active ocular lesions in 50 people , 36% of the patients experienced conversion of active to inactive lesions at 6 weeks.

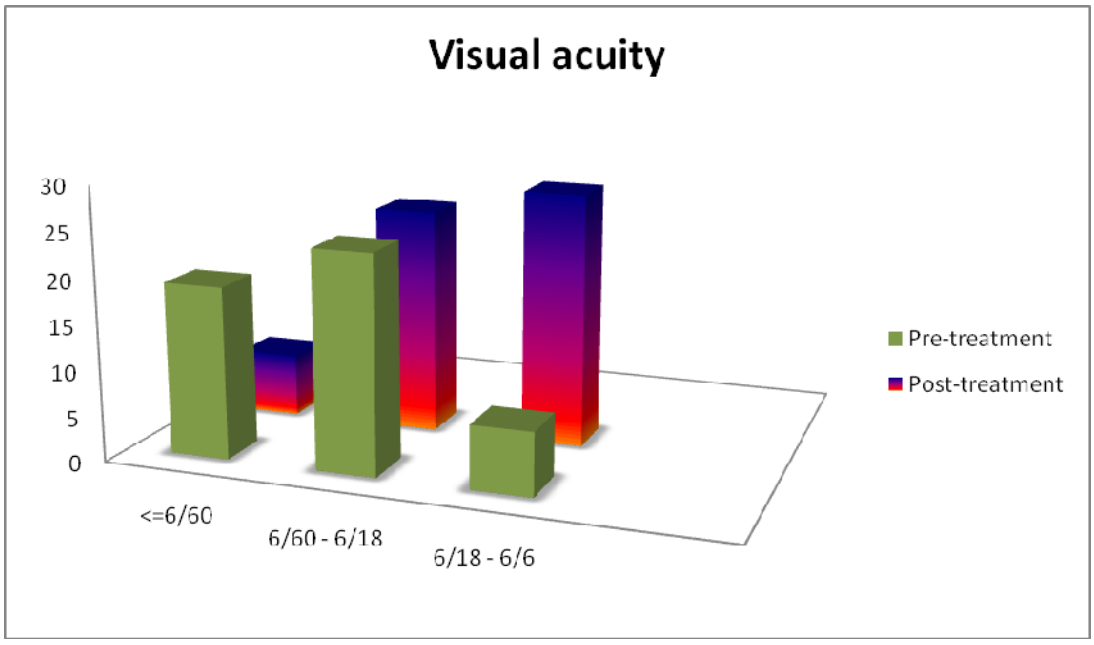
PRE-TREATMENT VISUAL ACUITY

Visual Acuity	No. of patients	Percentage
<=6/60	19	38
6/60 – 6/18	24	48
6/18 – 6/6	7	14

POST TREATMENT VISUAL ACUITY

Visual Acuity	No. of patients	Percentage
<=6/60	7	14
6/60 – 6/18	25	50
6/18 – 6/6	18	36

COMPARISON BETWEEN PRE AND POST TREATMENT VISUAL ACUITY IN OCULAR TOXOPLASMOSIS

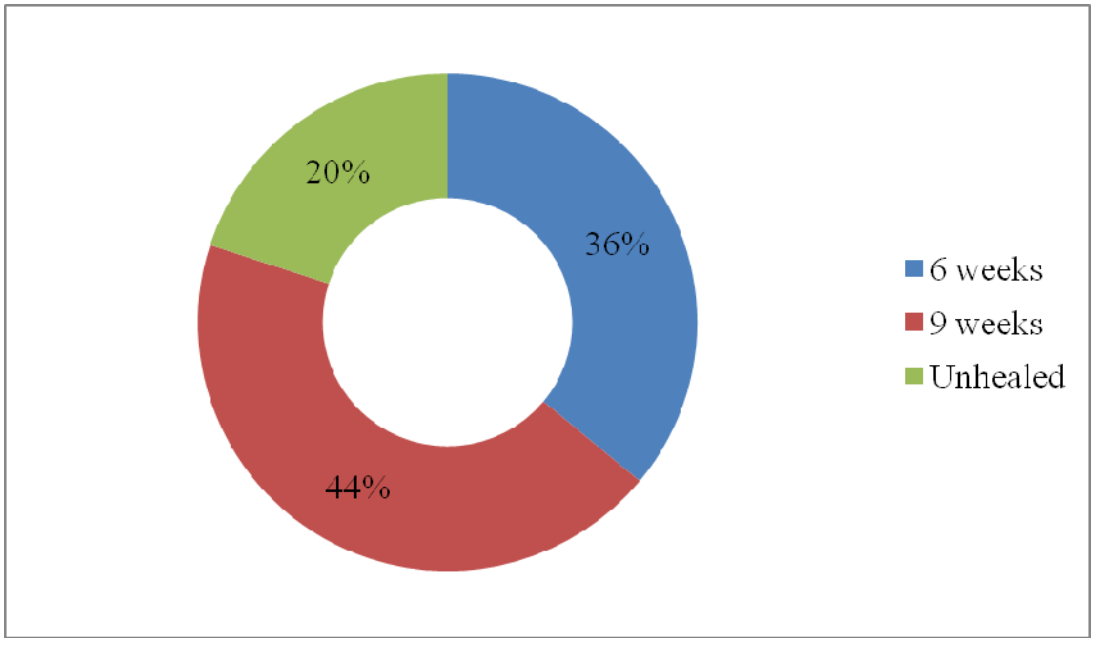


There was a distinct improvement in visual acuity of the patients.There was a decline in the percentage of people with a visual acuity of <=6/60 from 38% to 14% whereas, people with an acuity between 6/18 to 6/6 increased from 14% to 36%.The section of people with with visual acuity between 6/60 to 6/18 changed marginally from 48% to 50%.

EFFICACY OF AZITHROMYCIN

	Lesions healed at 6 weeks	Lesions healed at 9 weeks	Unhealed lesions at 9 weeks
No. of patients	18	22	10

CHART SHOWING HEALING TIME OF LESIONS



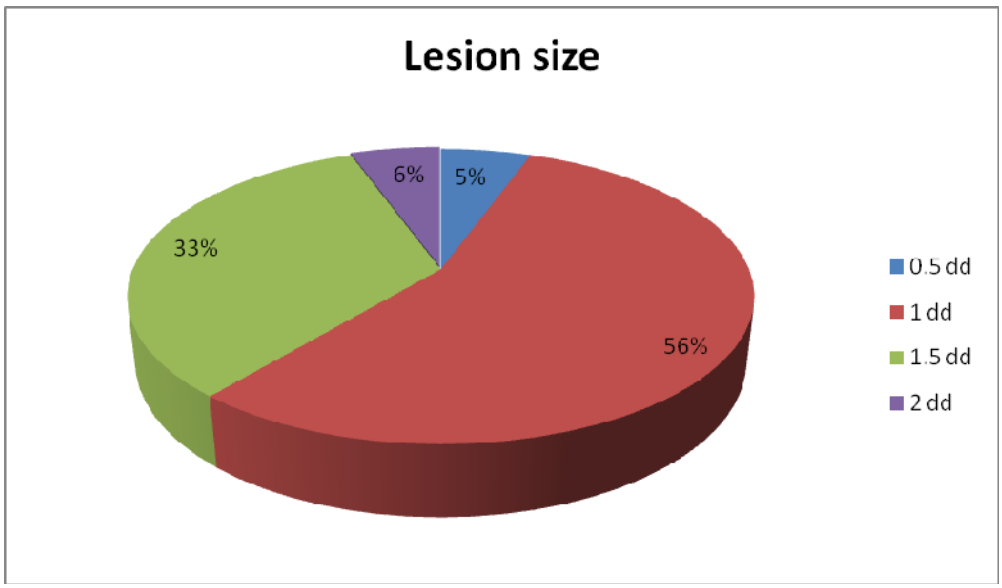
CHARACTERISTICS OF LESIONS HEALED AT 6 WEEKS

Total no. of patients - 18

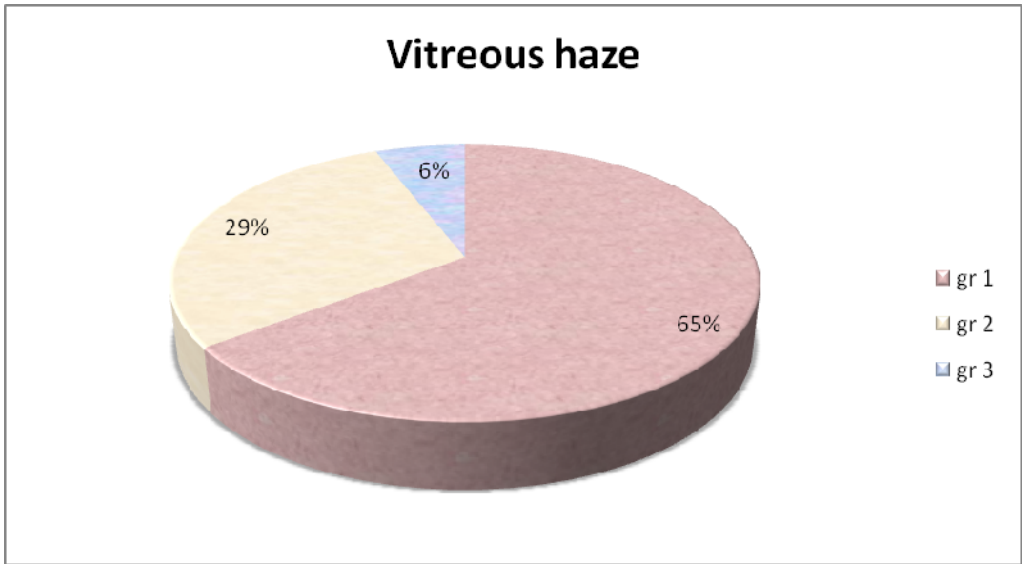
Lesion size	0.5 dd	1 dd	1.5 dd	2 dd
No.of patients	1	10	6	1

Vitreous haze	Gr 1	Gr 2	Gr 3
No. of patients	11	6	1

Of the patients whose treatment was considered as therapeutic success ,56% had a lesion size of 1 dd and only 2% had a size of 2 dd. The majority i.e 61% had a vitreous haze of grade 1.



Majority of the patients with healed lesions(56%) had lesions corresponding to 1 dd ,followed by 33% with lesions of 1.5dd.Only 6% had lesions of 2 dd.



Most of the patients in this group (65%) had a vitreous haze of grade 1 followed by 29% with that of grade 2.

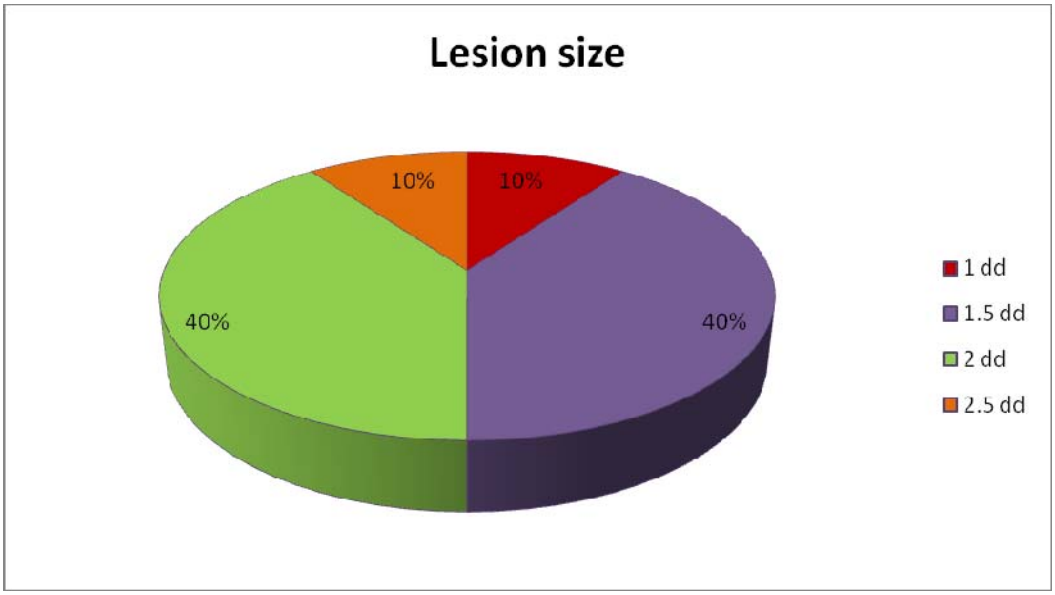
CHARACTERISTICS OF LESIONS NOT RESOLVED AT 9 WEEKS

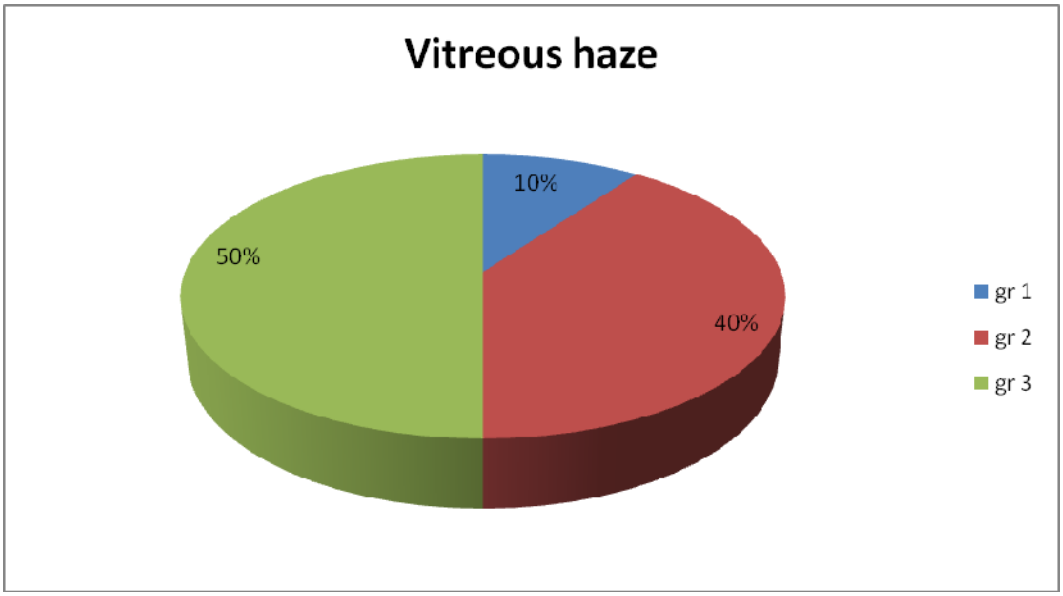
Total no. of patients - 10

LESION SIZE	1 dd	1.5 dd	2 dd	2.5 dd
No. of patients	1	4	4	1

Vitreous haze	**Grade 1**	**Grade 2**	**Grade 3**
Total no. of patients	1	4	5

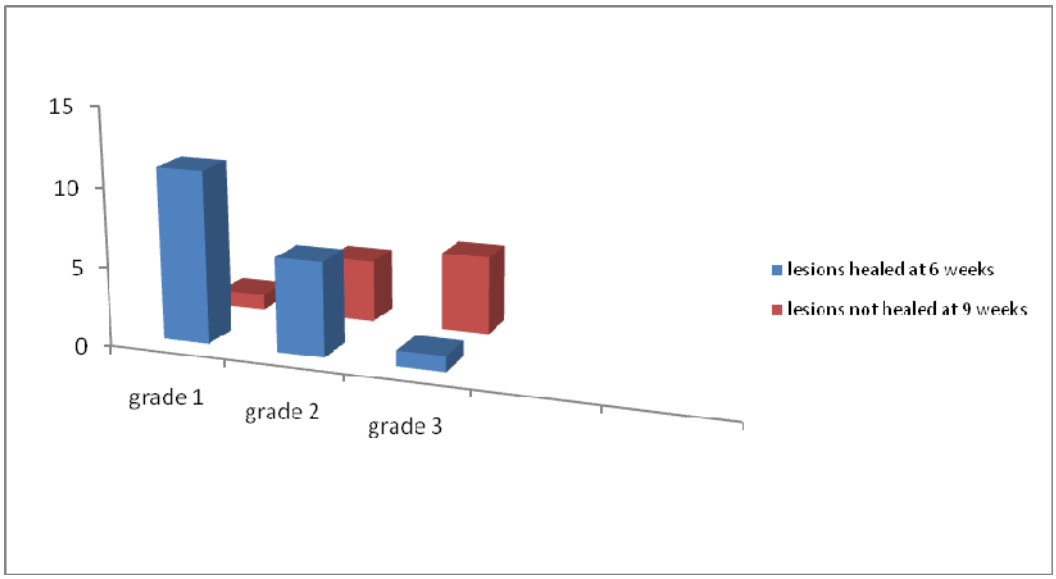
Out of 10 patients with unresolved lesions even at 9 weeks, 40% had a lesion size of 1.5 and 40% of 2 dd. 50% had a vitreous haze of grade 3 and 40% of grade 2.



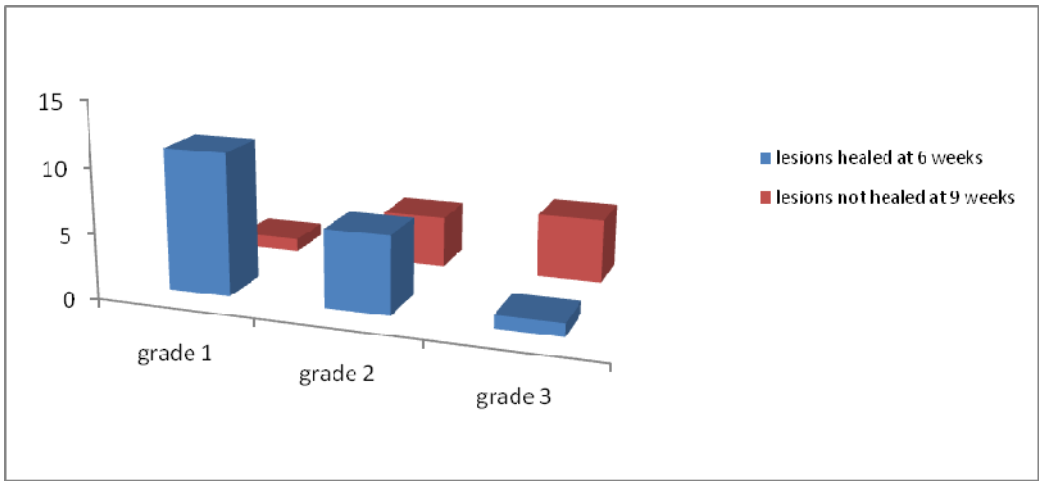


Majority of the patients in this group had lesions of size of 1.5 and 2 dd.(40% each) and 50% had a vitreous haze of grade 3.

COMPARISON OF THE LESIONS HEALED AT 6 WEEKS WITH LESIONS UNHEALED AT 9 WEEKS



Most of the lesions which healed by 6 weeks (therapeutic effect of the drug) were in the range of 1 and 1.5 dd.Most of the lesions which did not heal even at 9 weeks were of 1.5 and 2 dd.



Most of the lesions healed at 6 weeks were associated with a vitreous haze of grade 1 while those which did not heal at 9 weeks had a haze of grade 3 mostly.

DISCUSSION

Ocular toxoplasmsis is one of the most frequently identified causes of uveitis and Toxoplasma gondii remains the most common organism to infect the retina in an otherwise healthy individual.[32, 33]

This prospective ,non randomized clinical study lasting for one and half years was done to evaluate the efficacy of oral Azithromycin the treatment of ocular toxoplasmosis.

The main aim was to measure the reduction in intraocular inflammation and change in the morphology of the retinal lesion at the end of 6 weeks and to look for recurrence of lesions at new sites at the end of 6 months.The differences in the characteristics of lesions responding to the drug at the end of 6 weeks and those not healing by 9 weeks were also studied.Apart from this ,the improvement in visual acuity at the end of 6 weeks and 9 weeks were also studied.

Out of all the patients included in the study 52% were in the age group 21 -40 years, 32% in the age group <20 years,12% in the group 41 – 60 years and 4% in the group above 60 years. This was in conjunction with a 1973 publication wherein Perkins claimed that ocular toxoplasmosis was most common in the second and third decades of life.[26]

The ratio of males to females was almost equal ,with males being at 52% and females at 48%.A study done by Rothova et al on 14 patients showed similar findings.[25]

The chief ocular symptom with which the patients presented (66%) was defective vision. The reasons for this could be the location at macula,macular oedema , large lesion size and prescence of intense

inflammation. This was followed by floaters (19%), caused due to opacities in the vitreous. Redness, pain and photophobia were present in only in 15% of the patients who presented with a spill over anterior uveitis.

The majority of the patients (70%) did not have any anterior segment involvement.30% did show some features of involvement of anterior segment.

A study done by G.N Holland on 10 patients shows that patients with acquired Toxoplasma gondii infection can present with intraocular inflammatory reactions without co-existing necrotizing retinal lesions.[34]Therefore this factor should be borne in mind.

Almost half of the patients (40%) had a vitreous haze of grade 2,followed by 30% having a haze of grade 1 and 24% having grade 3.Since vitreous haze is due to a hypersensitivity response along with others like anterior uveitis, vasculitis and retinal oedema, it can depend on various factors like strain of T. gondii and the host's immune response.

The most common location of the retinal lesion was the macula(44%) followed by that in the vicinity of blood vessels (28%). Juxtapapillary

lesions were present in 8% and lesions along the papillomacular bundle in 6%. Lesions located at locations elsewhwere on the retina were present in 8% and 6% had multiple lesions.

In another study conducted by Mets, Holfels and Boyer it was found that macular lesions occured in over 76% of the patients.[29] The increased occurrence of lesions at the macula is explained by a number of theories. One of them states that fetal vasculature develops first at posterior pole and is composed of end arterioles ,so infection is more likely to manifest here.Another theory states that the parasite invades the eye through the Posterior Ciliary arteries and the optic nerve, therefore the frequent involvement of posterior pole.[30]

Main Outcome measures:

Vitreous haze: Intraocular inflammation reduced in a substantial number of patients , manifested by a decrease in the vitreous haze. 36% had a complete disappearance of inflammation. The number of people with grade 3 vitreous haze decreased by 18% , grade 2 by 12%, and grade 1 by 6%.Amongst the patients who manifested active disease at 6 weeks , the majority had a haze of grade 2.

Retinochoroidal lesion morphology : After 6 weeks of treatment 36% of the patients displayed inactive lesions ,but 64% still had active lesions. The persistently active lesions were associated with a larger initial size, more surrounding oedema and greater initial inflammation in the vitreous.

This is supported by a 1993 study conducted in Netherlands on 149 patients. The patients were divided in four groups.The first group was treated with combination of Pyrimethamine, Sulfadiazine, corticosteroids.The second with Clindamycin,Sulfadiazine and corticosteroids and the third with Trimethoprim ,Sulfamethoxazole and corticosteroids.The last group had peripheral lesions and was not put on any treatment. They discovered that there was no difference in the duration of inflammatory activity between the treated and untreated groups or between separate groups of treated patients.Therefore the most important factor predicting the duration of inflammatory activity was the size of the lesion itself ,independent of the treatment.[l24]

36% of the active lesions healed in 6 weeks time and these were termed as therapeutic success.44% healed in 9 weeks which was attributed to the body's immune mechanism , since this is the time taken by the lesion to

heal in an immunocompetent person.20% of the lesions remained active even after 9 weeks.

Out of the patients who exhibited a good response to the treatment, most (56%) had retinal lesions of smaller size i.e 1 dd or less. The majority (65%) had a vitreous haze of grade 1. Only a minority i.e 6% had a lesion size of 2 dd or more and a vitreous haze of grade 3.This proved that lesions with a smaller size and associated with lesser inflammation responded better to the treatment than those with larger size and more inflammation.

Amongst the patients whose lesions were unresolved even at 9 weeks , 40% had a size of 1.5 dd and 40% of 2 or more dd.50% had a vitreous haze of grade 3 and 40% of grade 2. This showed that lesions of larger size and associated with greater inflammation did not respond effectively to the treatment.Their natural course went beyond 9 -10 weeks in many cases .

Visual acuity(VA) : Visual acuity of many patients showed a definite increase at 6 weeks, with 36% of the patients having an acuity between 6/18 and 6/6.However the majority (50%) had an acuity between 6/60 and 6/18, and a small minority still had an acuity of less than 6/60.

Most of the patients in the category where the vision was still 6/60 either had large macular lesions or those associated with intense inflammation. People who had vision between 6/60 and 6/18 included mostly those who had macular lesions which healed but resulted in a scar leading to persistently diminished vision. In the third category ,most of the lesions were located at places other than the macula or had a lesser grade of inflammation.

In a study done on 14 patients with acquired ocular toxoplasmosis, Rothova et al reported a final acuity of less than 20/200 in 6 patients because of location of retinal lesion (3 patients), phthisis (2 patients), and optic atrophy (1 patient).[34]

Some of the other complications resulting in reduced vision as reported by them include cataract, persistent vitreous opacities, ischemic retinal areas, optic nerve atrophy, retinal detachment and phthisis. In the 1993 study done on 149 patients in Netherlands, it was found that inspite of there being a marked reduction in the size of lesions in all the four groups, visual acuity before and after treatment did not differ much significantly.This was probably due to many lesions being at the macula and it being involved in residual scarring.[24]

At the end of 6 months ,there was no recurrence of lesions at newer locations. Of the 10 patients with unhealed lesions at 9 weeks ,7 had healed by 6 months with scarring, 2 showed evidence of consecutive optic atrophy and one still had minimum inflammation in the vitreous.

In the study carried out by Rothova et al , the inference drawn was that the risk of recurrence in postnatally acquired toxoplasmosis is 57% within 2 years. Moreover the recurrence rate increases with the length of follow up. Noteworthy was the fact that in five out eight patients with recurrences , initial lesions were greater than 3 dd compared to one of six patients without any recurrences. Traditionally recurrences have been associated with congenital toxoplasmosis[34].

A number of hypothetical triggers for reactivation or recurrence have been suggested which include, immune response and hormonal status of the host, human leukocyte antigen type, autoimmune or hypersensitivity reactions against the exposed toxoplasmic antigens and parasite related factors such as mechanical rupture of cyst caused by parasite multiplication ,release of lytic enzymes by the parasite and reinfection with other parasite strains.[34]

In a study carried out on 11 immunocompetent patients of ocular toxoplasmosis, treated with Azithromycin 500 mg on day one and followed by 250 mg /day for 5 weeks many of whom received additional Pyrimethamine, 3 patients developed recurrent lesions at 7, 8 and 9 months.[25]

The reason for there being no recurrences in our study could be probably that drug is active against the cyst form as recently proposed[20,21] at the dose used here. Also all the patients chosen in the study were immunocompetent and none of the lesions were as large as 3 dd like the study mentioned previously[34] Another factor is that 6 months is too short a time to comment on the incidence of recurrence and the patients need to be followed for a longer time.

CONCLUSION

Ocular toxoplasmosis is a very common disease in immunocompetent people and causes significant visual morbidity in a functionally productive population. Although mostly self limiting, to date prevention of recurrent attacks is not feasible[35]. as most of the drugs used are active against the tachyzoite form and spare the cyst form.

Azithromycin 500 mg b.d for a period of 3 weeks is well tolerated and has considerable efficacy in the treatment. In a disease like ocular toxoplasmosis which is essentially self limiting in most immunocompetent

individuals, antimicrobials should be prescribed only if truly justified.Azithromycin does bring about an earlier resolution (4-6 weeks) in a disease which would otherwise last for 10 weeks or longer and handicap the person.

However ,it seems that it has better action when the lesions are small and inflammation not very intensive. It is being proposed as one of the drugs apart from Atovaquone to be active against the cyst form of the parasite and therefore may prevent recurrences.[24] It is also devoid of any major side effects unlike the drugs used in the triple and quadruple regime.Azithromycin is also readily available and economically reasonable for most patients. All these points that to the fact that it is a reasonable alternative to the drugs and at times may even prove better than them.

This study is a small interventional study carried out on a small population for a short period of time. In order to judge the drug's true benefits and disadvantages a larger number of people should be followed for a longer time. Comparison studies with other treatment modalities are also needed. The aspect which needs to be addressed to with greater urgency is the prevention of recurrence as it is this which significantly compromises the patient's vision.

Finally, it must be emphasised that is no drug is perfect and all have their positive and negative aspects. The patient's response depends not only on the treatment but also on a variety of other factors like the organism's strain, host's immune response and lesion size.

Therefore keeping all these factors in mind, the disease requires greater research into its pathogenesis and search for a superior treatment.

s

PART III

PROFORMA

PATIENT INFORMATION

Name :

Age :

Sex :

Occupation :

OP No. :

Address :

Phone No. :

CHIEF COMPLAINTS

Defective vision

Floaters

Pain, Redness and Photophobia

Onset : Acute/Insidius/Chronic No. of attacks:

Systemic history : Fever/ joint pain/rashes /ulcers/diarrhoea

Past history : TB/Herpes/Diabetes/Hypertension/Trauma

Personal history : Drug allergy/Exposure to pets/Diet (veg/non veg)

SYSTEMIC EXAMINATION:

CNS

CVS

RS

GIT

ENT

SKIN

GENITOURINARY

OCULAR EXAMINATION	:	RE	LE
Visual acuity	:		
IOP (Applanation)	:		
Conjunctiva	:		
Cornea	:		
Iris	:		
Anterior chamber	:		
Lens	:		
Anterior Vitreous	:		

Fundus examination (90 D/IDO) :

- Vitreous haze grading
- Disc
- Vessels
- Macula
- Retinal lesion size
- Retinal lesion location
- Retinal periphery
- Other features
- Diagram

INVESTIGATIONS

CBC:

ESR:

Mantoux:

VDRL :

HIV ELISA:

TORCH Profile:

Chest X-ray :

RBS :

TREATMENT given:

T. Azithromycin 500 mg b.d

T.Prednisolone 1mg/kg body wt od

T. Ranitidine 150 mg b.d

Prednisolone acetate e/d (if anterior uveitis present)

2% Homatrpine e/d b.d (if anterior uveitis present)

FOLLOW UP

	Visual Ac.	Vitreous haze	Retinal lesion
Wk 1			
Wk 2			
Wk 3			
Wk 6			
Wk 9			
6 th month			
Recurrence +/-			

KEY TO MASTER CHART

VA : Visual acuity

IOP : Intra ocular pressure

VH : Vitreous haze

ph : pin hole

nip : not improving with pin hole

gr : grade

dd : disc diameter

fl. And dem. : flat and demarcated

Les. Morph : Lesion morphology

MC : Macular choroiditis

VAC: Vessel associated choroiditis

PMB C : Papillomacular bundle region choroiditis

JPC : Juxtapapillary region choroiditis

CE : Choroiditis elsewhere on the retina

MFC : Multifocal choroiditis

OMC : Old macular choroiditis

LIST OF SURGERIES PERFORMED

S..no.	Name	Age	Sex	Diagnosis	IP. No.	Surgeries
1.	Elangovan	55	M	RE MC/LE PSEUDOPH.	616432	RE ECCE with PCIOL
2.	Jayasheelan	60	M	BE IMC	628288	RE ECCE with PCIOL
3.	Aruna	53	F	RE IMC/LE MC	624351	LE ECCE with PCIOL
4.	Subramani	48	M	RE CHALAZION	678346	Incision and currettage
5.	Muniammal	57	F	BE IMC	698764	LE ECCE with PCIOL
6.	Lakshmi	62	F	BE MC	615432	RE ECCE with PI
7.	Mary	54	F	RE IMC	626254	LE ECCE with PCIOL
8.	Venkatesh	68	M	RE ENDOPHTHAL	658933	RE Intravitreal antibiotics
9.	Babu	50	M	LE IMC	678454	LE ECCE with PCIOL
10.	Chandra	56	F	LE CDC	678456	LE DCT
11.	Kanniappan	72	M	RE MC	645432	RE ECCE with PCIOL
12.	Selvi	38	F	RE EXP. KERATITIS	623543	RE Medial Tarsorrhaphy
13.	Abdul . R	52	M	LE IMC/RE PSEUDOPH.	634536	LE SICS with PCIOL
14.	Dhanalakshmi	65	F	BE IMC	678767	RE SICS with PCIOL
15.	Sunanda	57	F	LE MC/RE IMC	645367	LE SICS with PCIOL
16.	Jayammal	68	F	BE IMC	657345	RE SICS with PCIOL
17.	Lavanya	60	F	LE CDC	657473	LE DCT
18.	Arulraj	69	M	BE MC	698867	LE ECCE with PCIOL
19.	Varadhan	75	M	LE MC/RE PSEUDOPH.	656787	LE SICS with PCIOL
20.	Sumathy	47	F	RE CDC	619886	RE DCR
21.	Ranjitham	67	F	BE IMC	654334	RE SICS with PCIOL
22.	Rani	62	F	LE IMC	678765	LE SICS with PCIOL
23.	Manickam	75	M	RE MC/LE PSEUDOPH.	687890	RE SICS
24.	Krishnan	77	M	BE MC	633456	LE SICS with PCIOL
25.	Ayesha bee	60	F	RE IMC	676547	RE SICS with PCIOL

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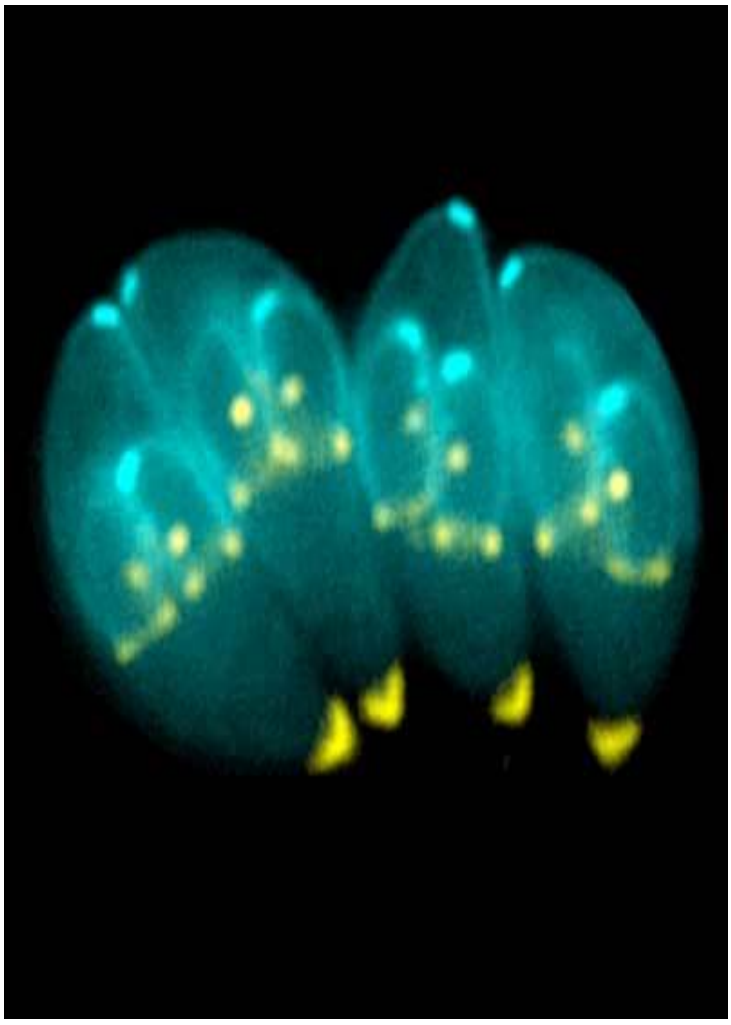
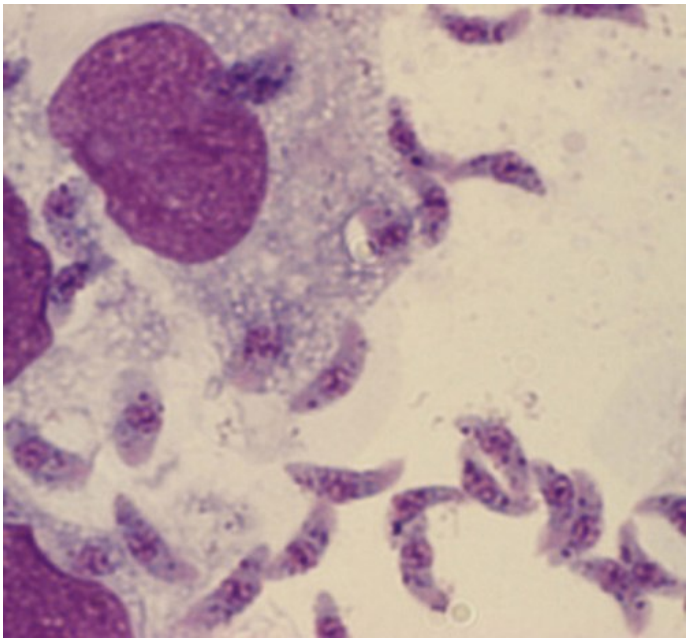
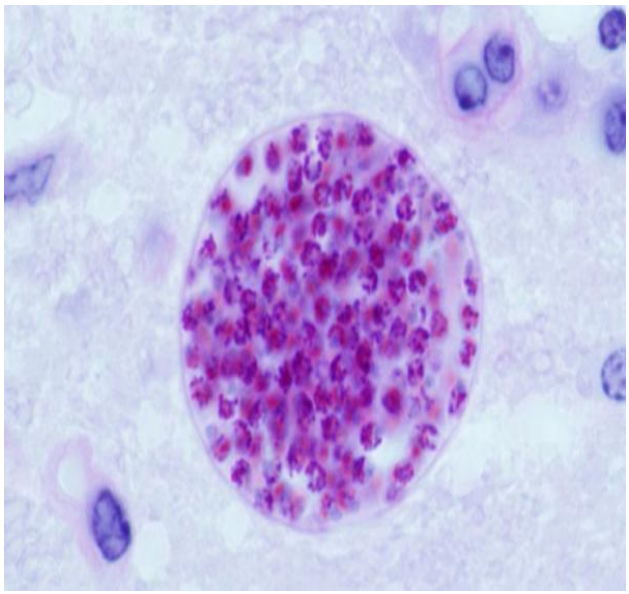


TOXOPLASMA GONDII



TACHYZOITES



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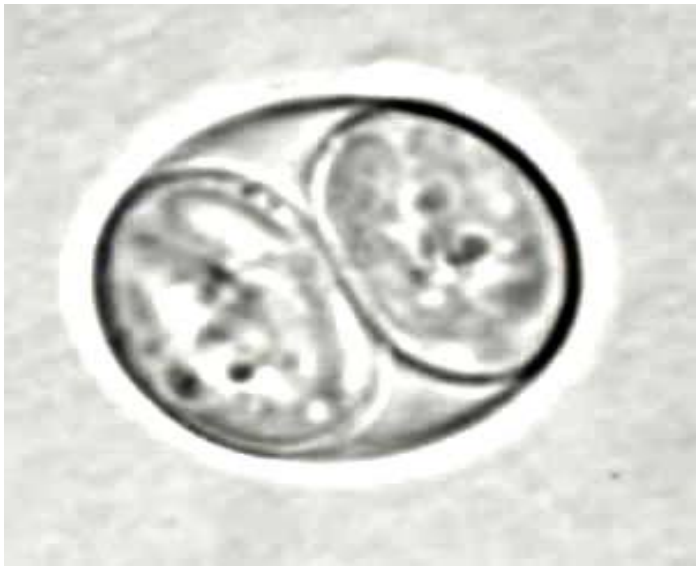
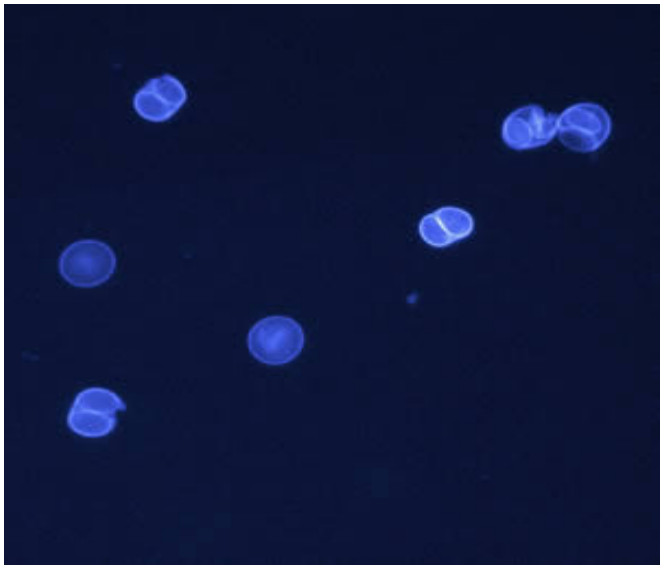
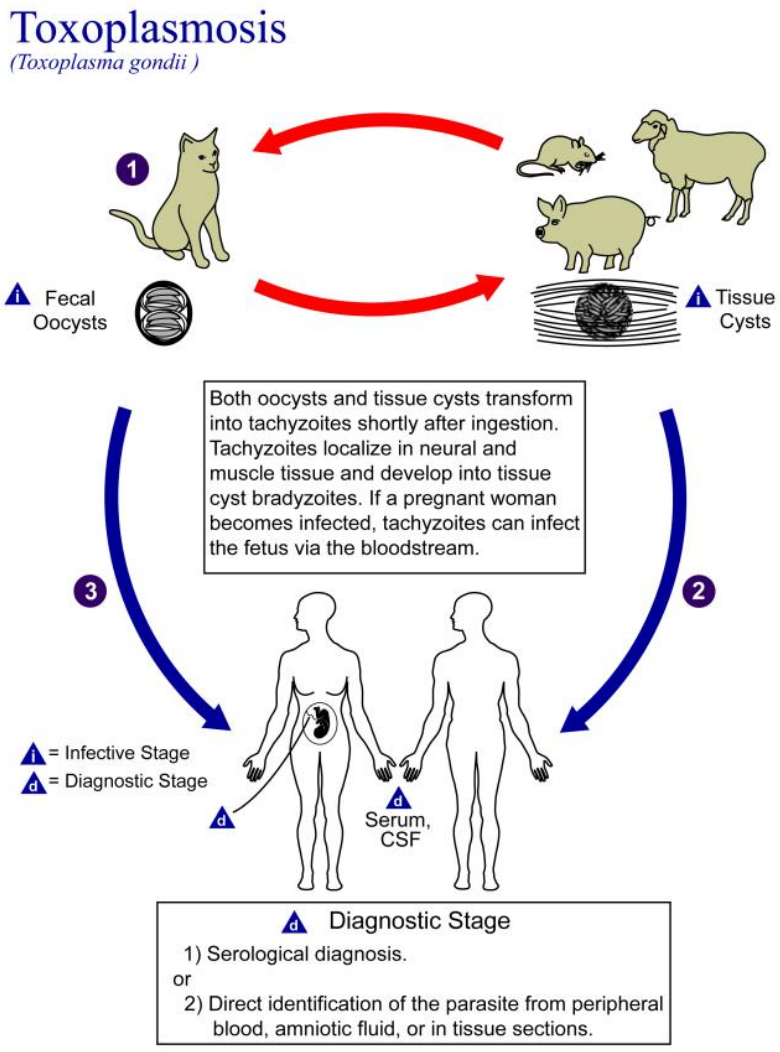


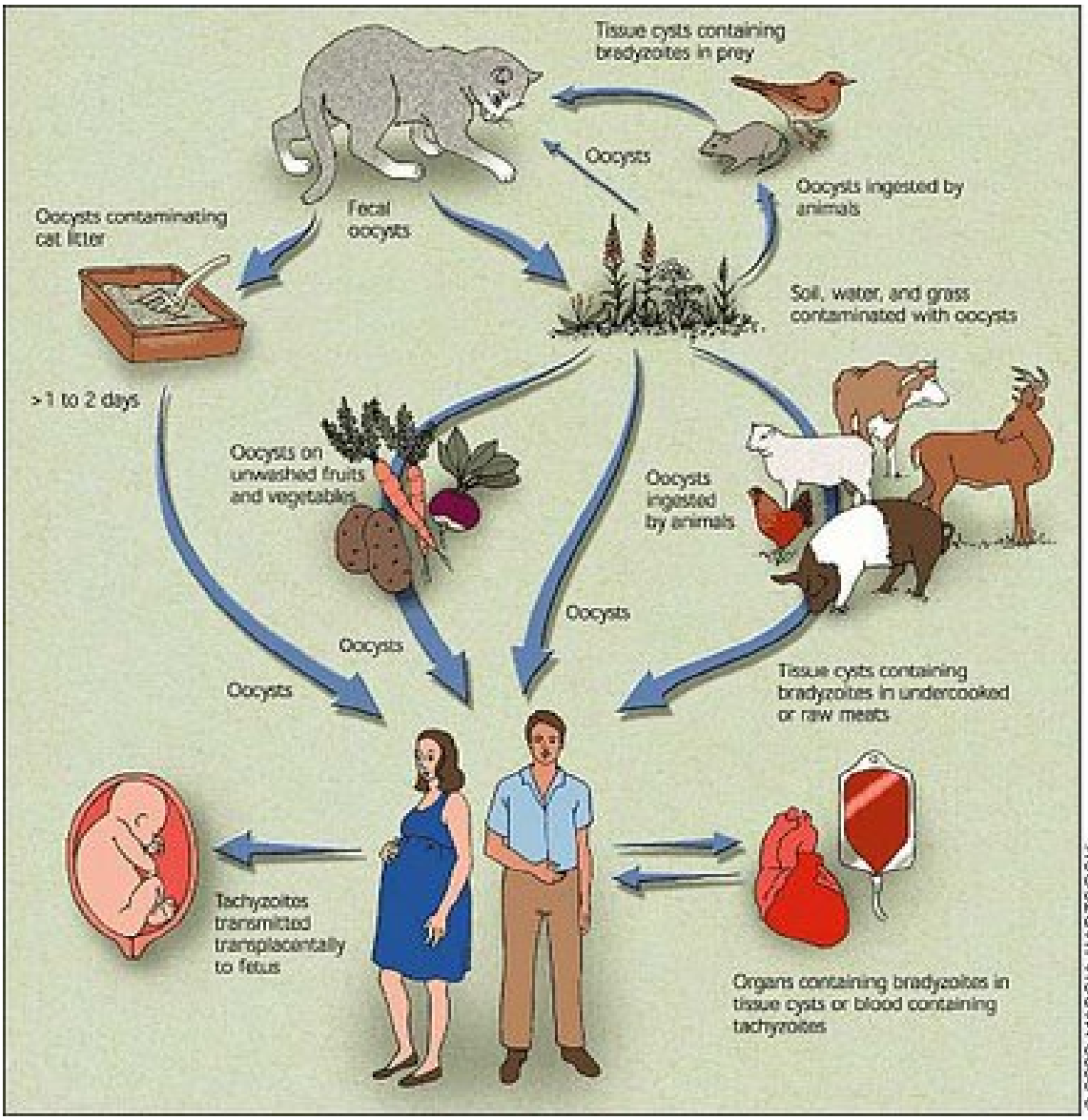
OOCYST



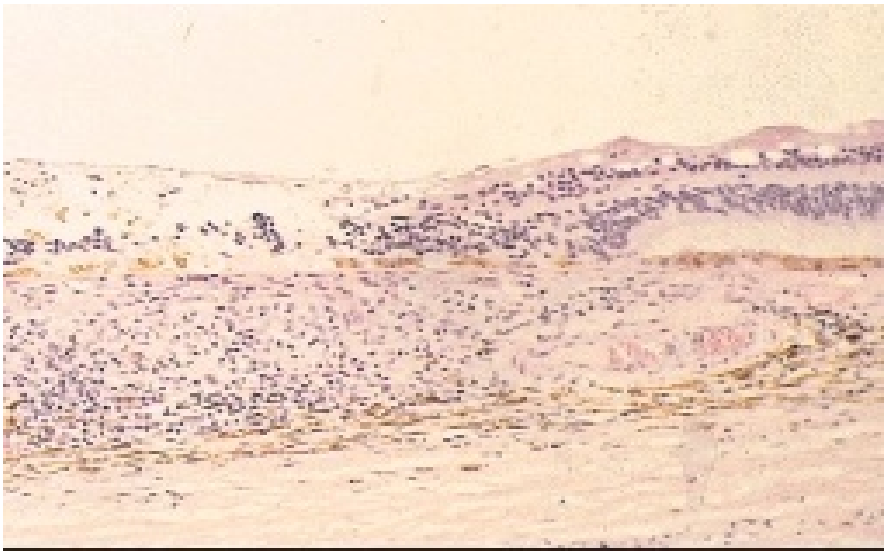
FECAL OOCYSTS – SPORULATED AND UNSPORULATED



LIFE CYCLE OF TOXOPLASMA GONDII



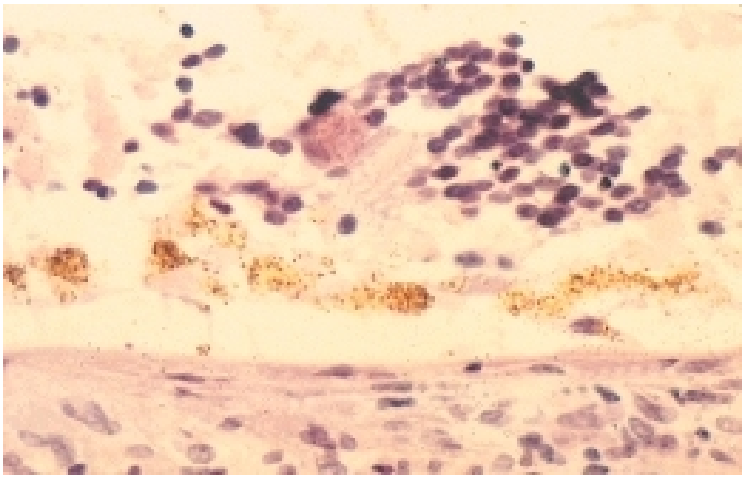
MODES OF TRANSMISSION OF INFECTION



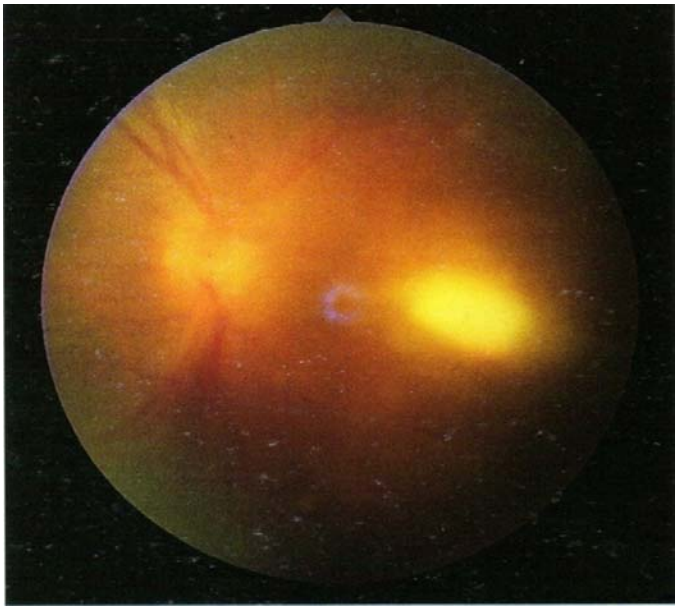
HISTOLOGY SECTION

ACUTE COAGULATIVE NECROSIS OF RETINA

SECONDARY DIFFUSE GRANULOMATOUS INFLAMMATION OF CHOROID

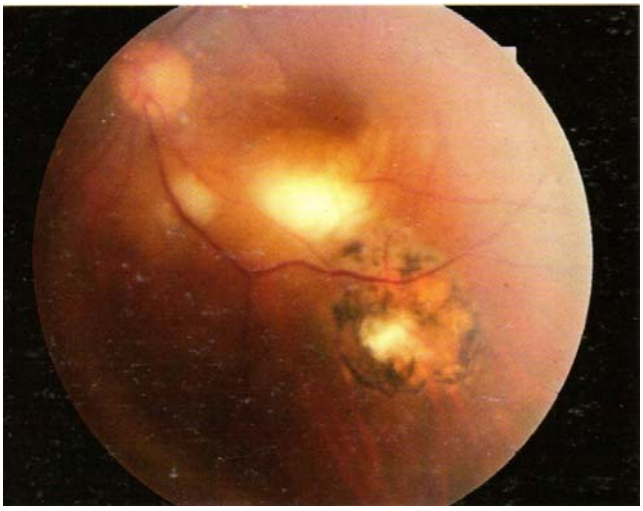


TOXOPLASMA CYSTS IN NEURAL RETINA



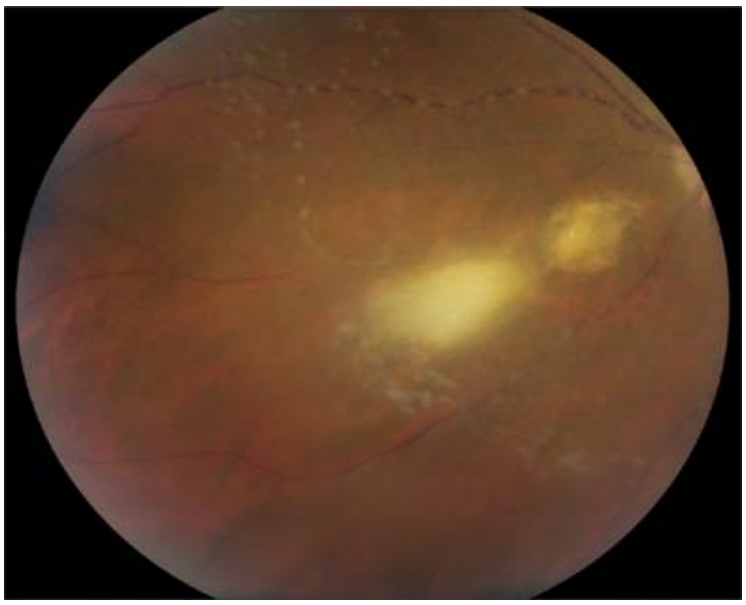
ACTIVE RETINOCHOROIDITIS WITH VITRITIS

'HEADLIGHT IN THE FOG APPEARANCE'



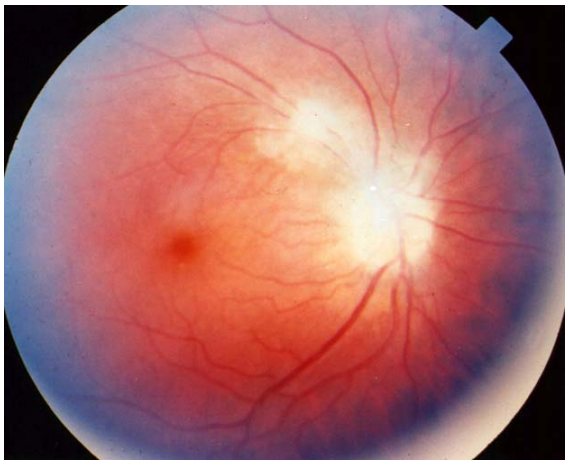
ACTIVE RETINOCHOROIDITIS PATCH NEXT TO AN OLD

CHOROIDITIS SCAR

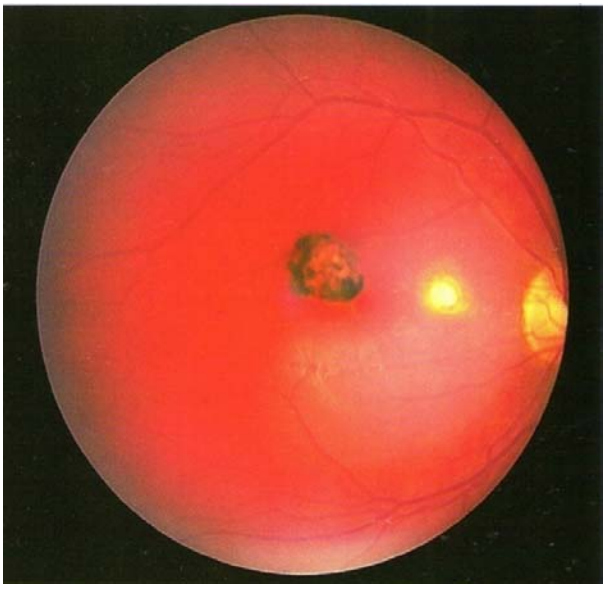


SHEATHING OF VESSELS WITH PLAQUES

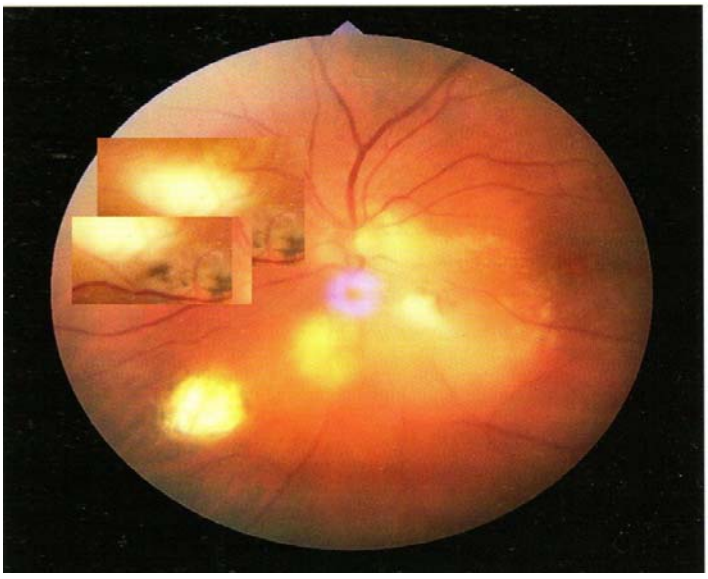
'KYRIELEIS ARTERIOLITIS'



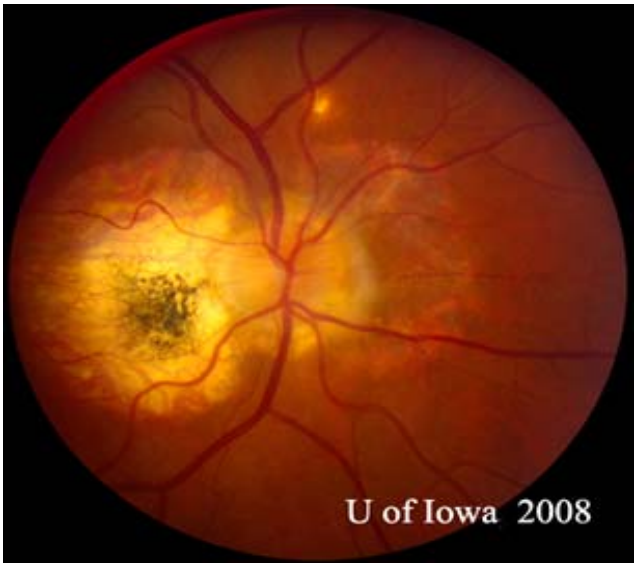
PAPILLITIS ASSOCIATED WITH RETINOCHOROIDITIS



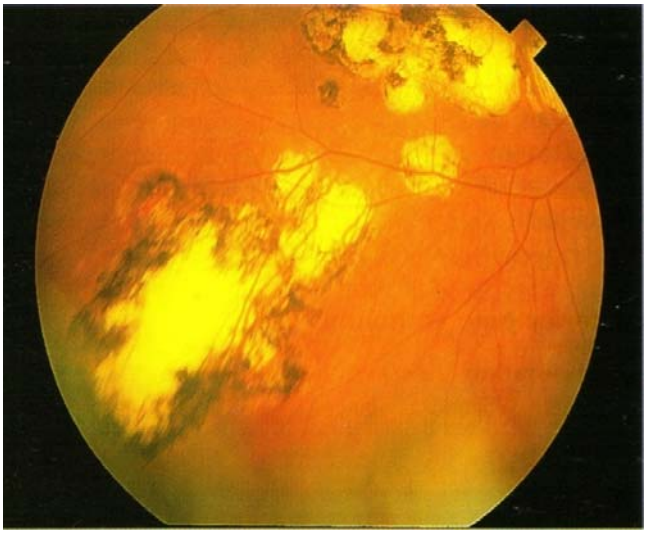
LESION INVOLVING PAPILLOMACULAR BUNDLE



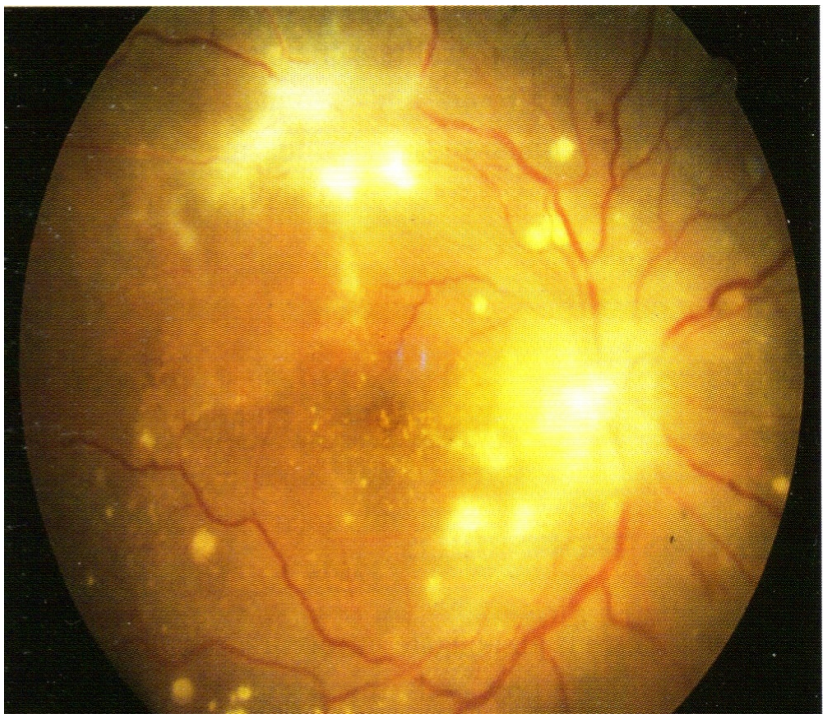
JUXTAPAPILLARY RETINOCHOROIDITIS



JUXTAPAPILLARY CHOROIDAL NEOVASCULAR MEMBRANE

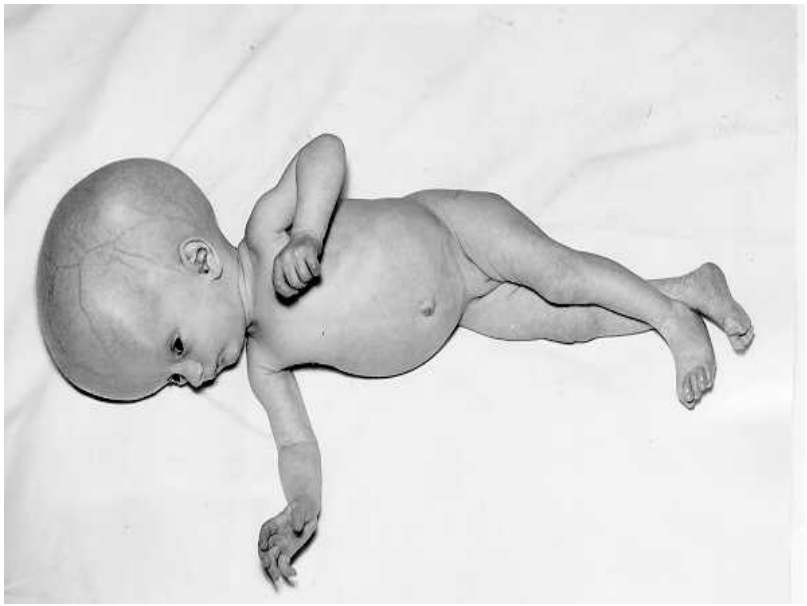


CONFLUENT RETINAL SCARRING DUE TO CHOROIDITIS

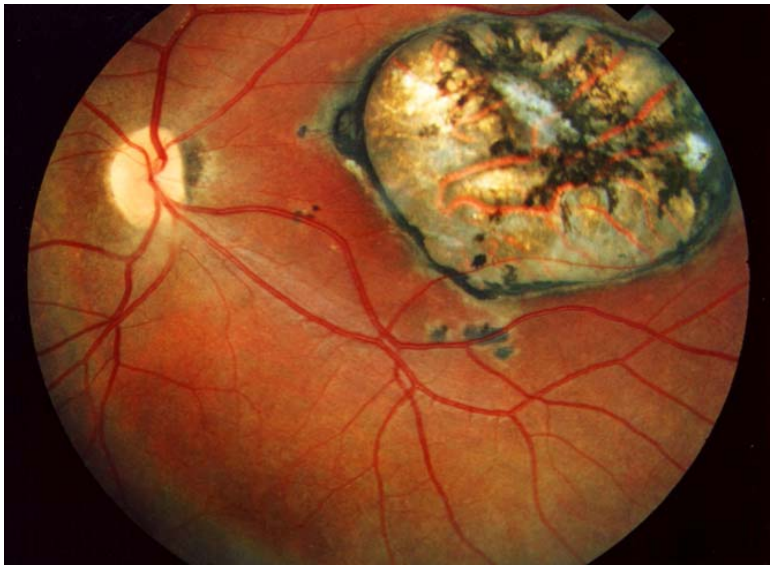


ATYPICAL MULTIFOCAL RETINOCHOROIDITIS IN THE IMMUNOCOMPROMISED

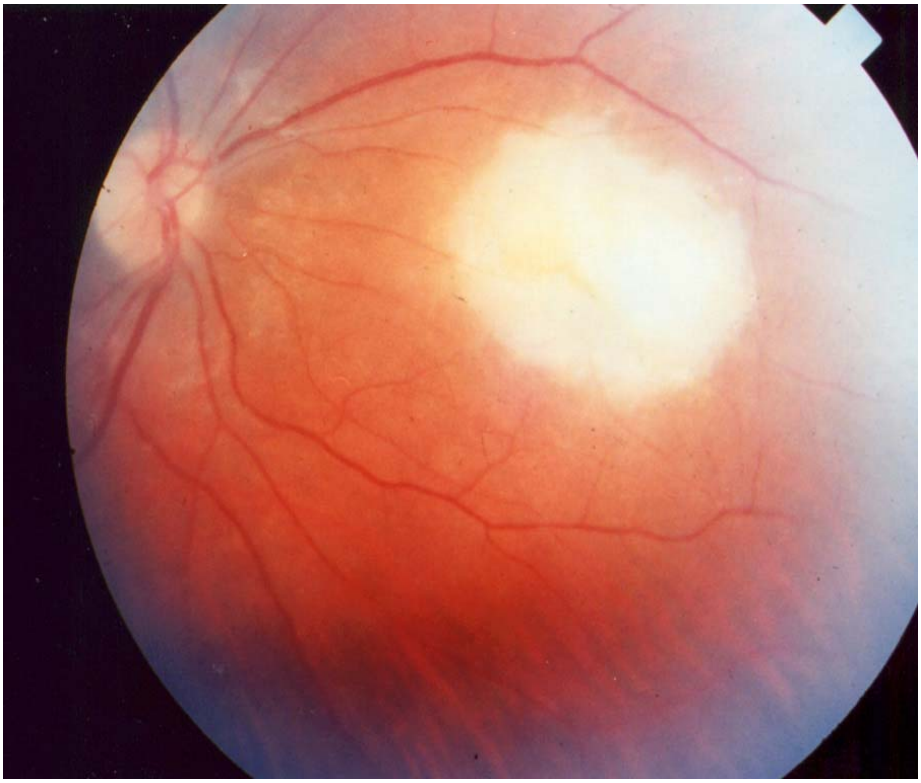
CONGENITAL TOXOPLASMOSIS



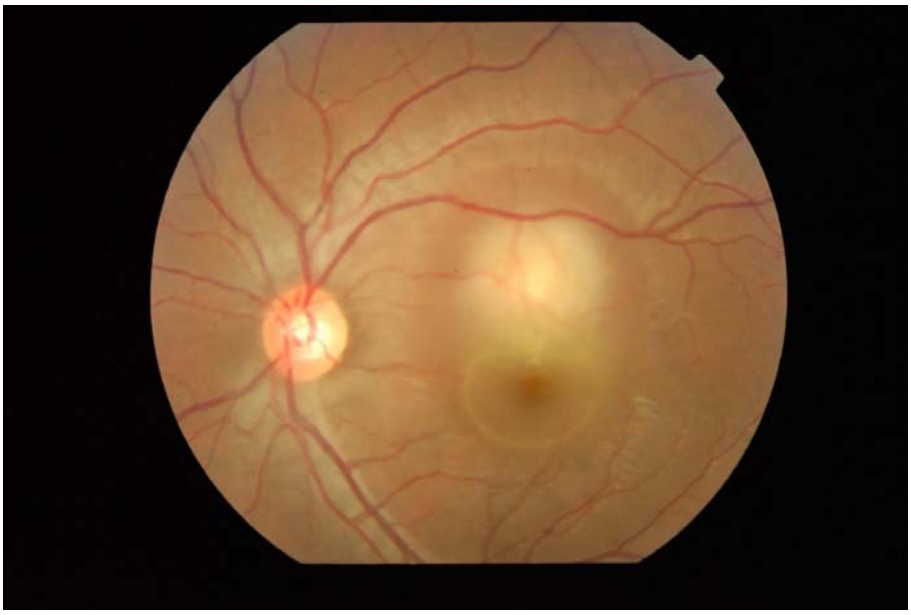
HYDROCEPHALUS AND HEPATOSPLENOMEGALY



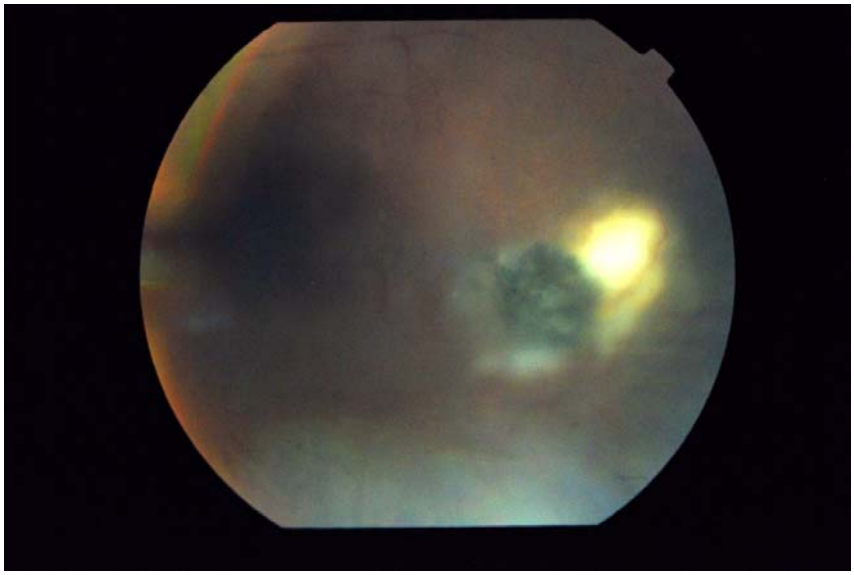
PUNCHED OUT MACULAR CHOROIDITIS SCAR



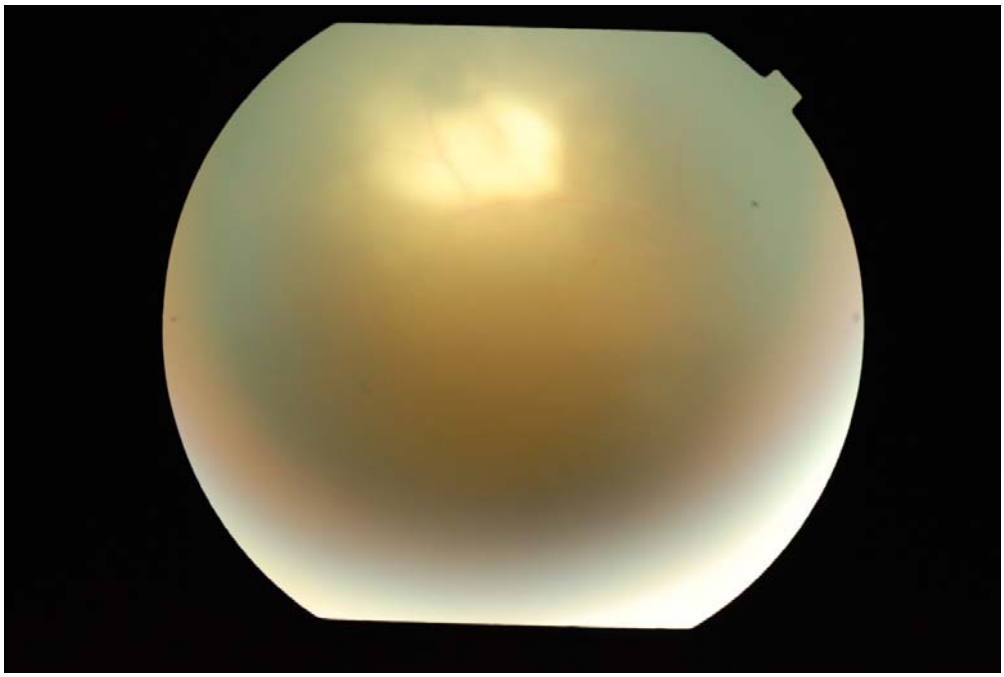
ACQUIRED TOXOPLASMOSIS - RETINOCHOROIDITIS WITH NO ASSOCIATED SCAR



ACTIVE RETINOCHOROIDITIS NEAR THE VASCULAR ARCADE

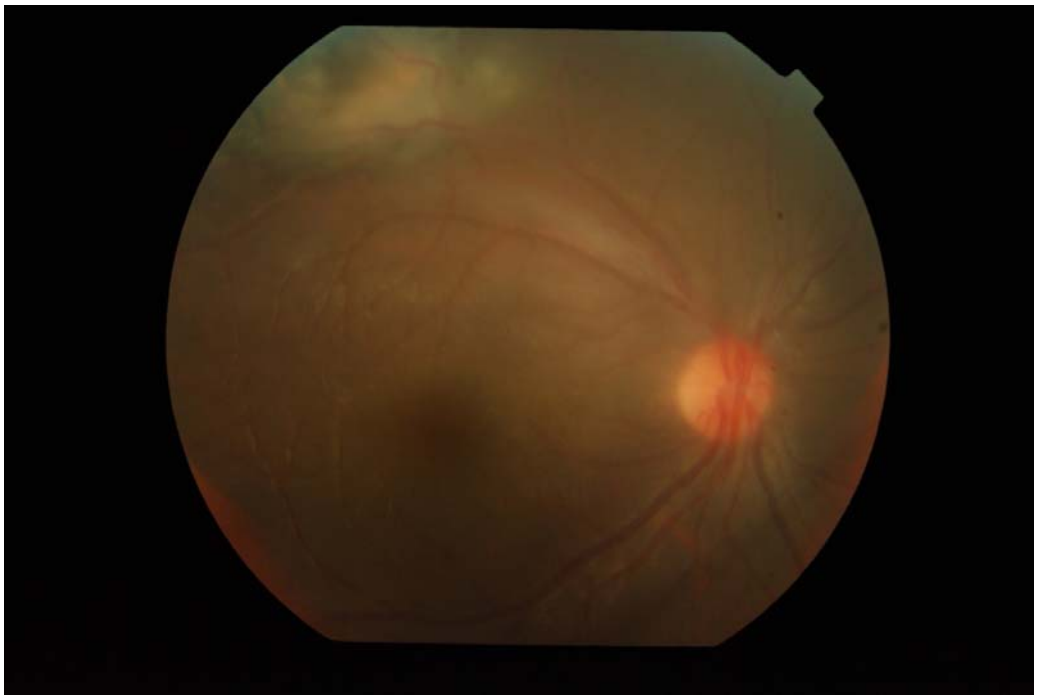


RETINOCHOROIDITIS NEXT TO AN OLD SCAR



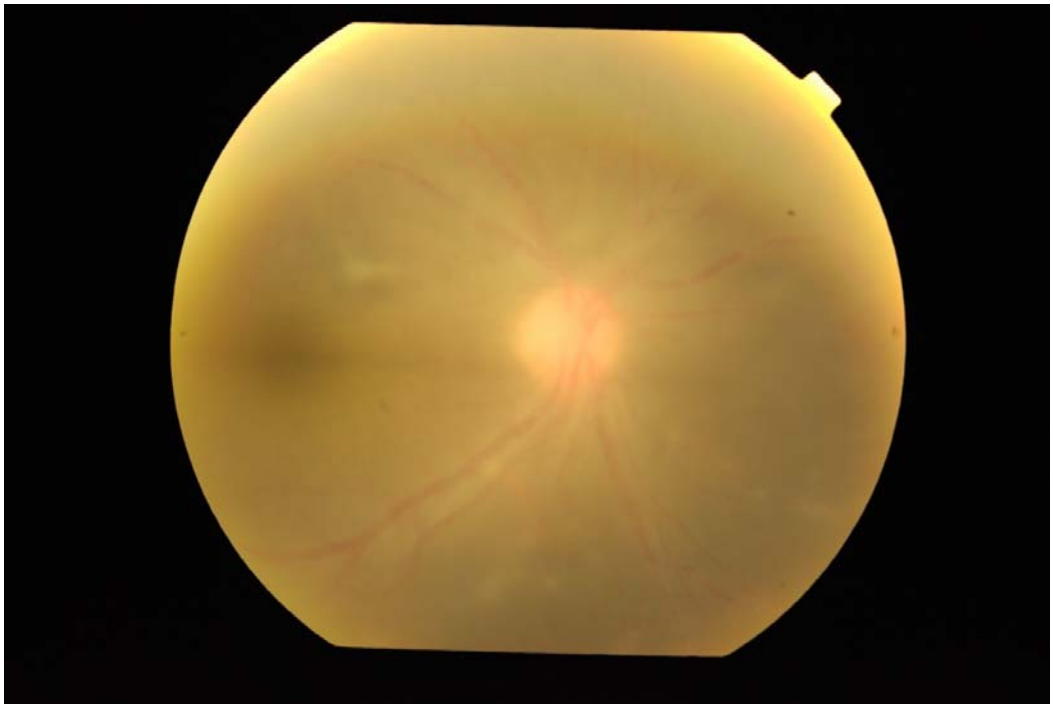
PRE TREATMENT FUNDUS PICTURE

ACTIVE RETINOCHOROIDITIS WITH ILL DEFINED MARGINS AND GRADE 3 VITREOUS HAZE

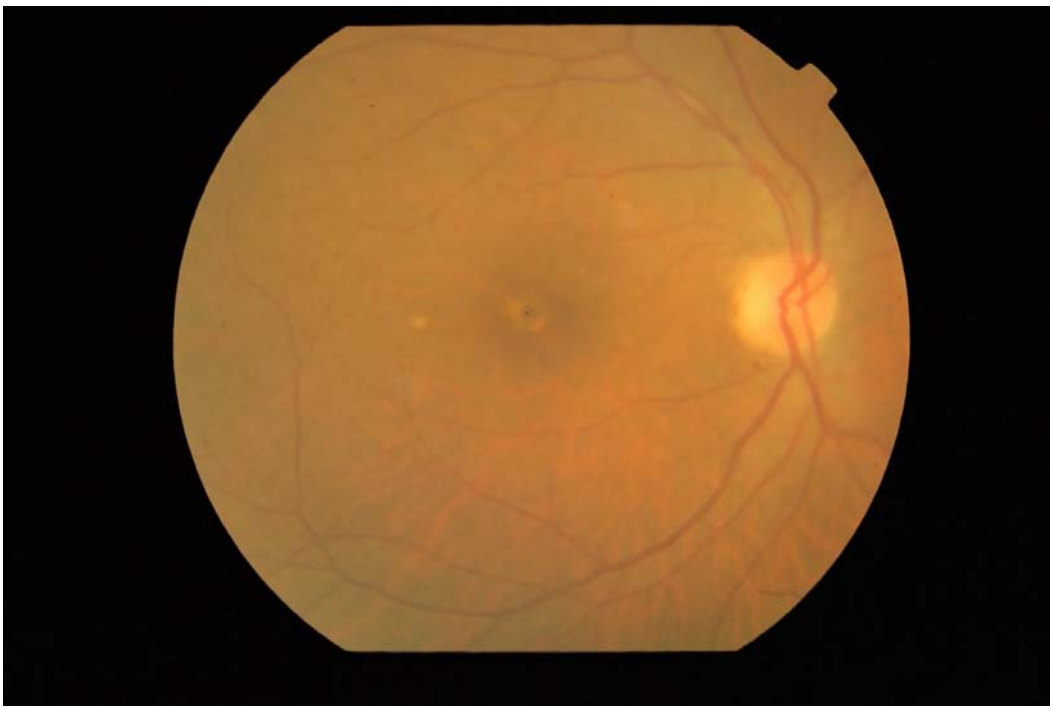


POST TREATMENT FUNDUS PICTURE AT 6 WEEKS

FLAT AND DEMARCATED INACTIVE LESION WITH NO VITREOUS HAZE



PRETREATMENT ACTIVE CHOROIDITIS PATCH NEAR THE MACULA WITH A VITREOUS HAZE OF GRADE 2



POST TREATMENT HEALED RETINOCHOROIDITIS PATCH WITH NO VITREOUS HAZE

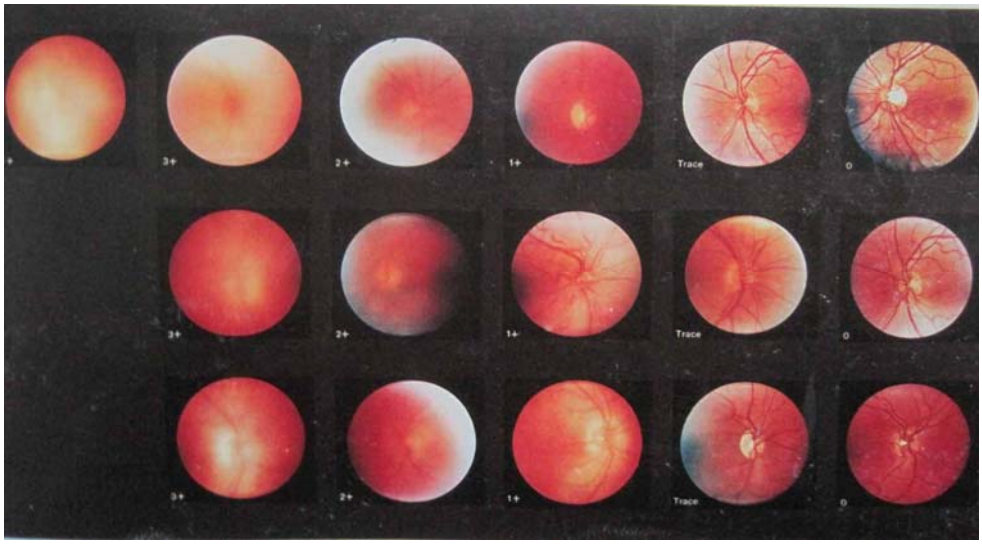


CHART DEPICTING GRADING OF VITREOUS HAZE
(NUSSENBLATT'S METHOD)

MASTER CHART

NAME	AGE	SEX	DIAGNOSIS		VA AT PRESENTATION		VIT. HAZE	LESION SIZE	IOP		TREATMENT	POST TREATMENT									New lesions
			RE	LE	RE	LE			RE	LE		3W				6 w			9w		6 months
												VN	VH	LES. MORPH	VA	VH	LES. MORPH	VA	VH	LES. MORPH	
Mainavati	49	F	N	m c	6/9 nip	1/60 nip	gr 2	2 dd	12	17	T.Azithro	6/60NIP	gr 2	active	6/60nip	gr 2	active	6/36	nil	fl and dem	nil
Vijay	19	M	N	jpc	6/6	6/24nip	gr 2	1 dd	12	11	T.Azithro	6/24nip	gr 2	active	6/18ph6/12	nil	fl. and dem.	6/18ph6/12	nil	fl and dem	nil
Kumuda	30	F	mc	N	6/60nip	6/9ph6/6	gr 3	2 dd	14	12	T.Azithro	6/60NIP	gr 2	active	6/36nip	gr 1	active	6/36ph6/24	nil	fl and dem	nil
Gangadurai	12	M	pmb c	N	6/36ph6/24	6/6	gr 2	1 dd	16	12	T.Azithro	6/24PH6/18	gr1	active	6/24ph6/18	nil	fl. and dem.	6/18nip	nil	fl and dem	nil
Satish	35	M	N	va c	6/12ph6/9	6/12nip	gr 1	1.5 dd	13	14	T.Azithro	6/12NIP	gr 1	active	6/12ph6/9	gr 1	active	6/12ph6/9	nil	fl and dem	nil
Kaniyapan	24	M	va c	N	6/24ph6/18	6/6	gr 2	2 dd	15	13	T.Azithro	6/24PH6/18	gr 2	active	6/24ph6/18	gr 1	active	6/24ph6/18	nil	fl and dem	nil
Edwin	25	M	N	va c	6/6	6/18nip	gr 1	1 dd	14	14	T.Azithro	6/18PH6/12	gr 1	active	6/18ph6/9	nil	fl. and dem.	6/18ph6/9	nil	fl and dem	nil
Asmat. U	20	M	o m c	va c	6/36nip	6/36ph6/24	gr 2	1.5 dd	12	12	T.Azithro	6/36NIP	gr 2	active	6/36nip	gr 2	active	6/36ph6/24p	nil	fl and dem	nil
Jyothi	15	F	N	m c	6/9ph6/6p	4/60nip	gr 3	2 dd	14	15	T.Azithro	5/60P	gr 2	active	5/60 p	gr 2	active	5/60nip	gr 2	active	nil
Muthulaksmi	17	F	N	va c	6/12ph6/9	6/12 nip	gr 1	1dd	12	13	T.Azithro	6/9P	gr 1	active	6/9ph6/6	nil	fl. and dem.	6/9ph6/6	nil	fl and dem	nil
Margatham	50	F	va c	N	6/24nip	6/12ph6/9	gr 2	1.5 dd	16	17	T.Azithro	6/24ph6/12	gr 2	active	6/24ph6/18	gr 2	active	6/24ph6/18	nil	fl and dem	nil
Manti devi	35	F	N	m c	6/9nip	6/60nip	gr 3	2 dd	13	15	T.Azithro	6/60PH6/36	gr 2	active	6/36ph6/24	nil	fl. and dem.	6/36ph6/24	nil	fl and dem	nil
Indira	29	F	N	m c	6/6	2/60nip	gr 2	2 dd	11	12	T.Azithro	3/60nip	gr 2	active	4/60nip	gr 2	active	4/60nip	gr 1	active	nil
Revathi	23	F	m c	N	6/60nip	6/12ph6/9	gr 3	1.5 dd	15	15	T.Azithro	6/60nip	gr 3	active	6/36nip	gr 3	active	5/60nip	gr 2	active	nil
Chitra	26	F	N	m c	6/6	6/36nip	gr 2	2 dd	12	12	T.Azithro	6/36nip	gr 2	active	6/24nip	gr 1	active	6/24nip#	nil	fl and dem	nil
Muthukumar	20	M	N	m c	6/6p	6/60nip	gr 2	3 dd	14	17	T.Azithro	6/60nip	gr 1	active	6/36ph6/24	gr 1	active	6/36ph6/24	nil	fl and dem	nil
Muthukrishnan	62	M	N	va c	6/9ph6/6p	6/12nip	gr1	0.5 dd	13	15	T.Azithro	6/12ph6/9	gr 1	active	6/9ph6/6p	nil	fl. and dem.	6/9ph6/6p	nil	fl and dem	nil
Ponnamal	35	F	N	va c	6/6p	6/36ph6/24	gr 2	1 dd	12	14	T.Azithro	6/36NIP	gr 2	active	6/36ph6/24	gr 2	active	6/36ph6/24	nil	fl and dem	nil
Elumalai	63	M	N	va c	6/9	6/24ph6/18	gr 1	1 dd	16	13	T.Azithro	6/24PH6/18	gr 1	active	6/18ph 6/9	nil	fl. and dem.	6/18ph6/9	nil	fl and dem	nil
Subhashini	16	F	c e	N	6/9ph6/6p	6/6	gr 1	1 dd	15	14	T.Azithro	6/9ph6/6	gr 1	active	6/9ph 6/6	gr 1	active	6/9ph6/6#	nil	fl and dem	nil
Gomati. D	14	F	j p c	N	6/18nip	6/6	gr 1	1 dd	13	18	T.Azithro	6/12ph6/9	gr 1	active	6/9nip	nil	fl. and dem.	6/9nip	nil	fl and dem	nil
Sabri	30	F	m c	N	6/60nip	6/6p	gr 3	2.5 dd	16	17	T.Azithro	6/60nip	gr 2	active	6/36pnip	gr 2	active	6/36nip	gr 1	active	nil
Leena	35	F	N	va c	6/6p	6/24nip	gr 2	2 dd	15	13	T.Azithro	6/24nip	gr 1	active	6/24ph6/18	gr 1	active	6/24ph6/18	nil	fl and dem	nil
Narayan.S	30	M	mult. C	N	6/24ph6/18	6/6p	gr 2	1-1.5 dd	14	14	T.Azithro	6/24nip	gr 2	active	6/24ph6/18p	gr 1	active	6/24ph6/18	gr 1	active	nil
Mahalakshmi	28	F	m c	N	6/60nip	6/9nip	gr 2	2 dd	17	18	T.Azithro	6/36nip	gr 2	active	6/36ph6/24p	gr 2	active	6/24nip	nil	fl and dem	nil
Mani	58	M	N	m c	6/24nip	6/60nip	gr 3	0.5-1 dd	14	12	T.Azithro	6/60nip	gr 2	active	6/60 nip	gr 1	active	6/60nip	nil	fl and dem	nil
Meena	19	F	va c	N	6/24ph6/18	6/6	gr 2	1 dd	11	13	T.Azithro	6/12nip	gr 1	active	6/12ph6/9	nil	fl. and dem.	6/12ph6/9	nil	fl and dem	nil
Muthu	29	M	N	m c	6/6p	3/60p	gr 2	2 dd	16	12	T.Azithro	3/60ph5/60	gr 2	active	5/60nip	gr 2	active	5/60nip	nil	fl and dem	nil
Ram	37	M	N	c e	6/12ph6/9	6/24ph6/18	gr 1	1.5 dd	14	18	T.Azithro	6/18nip	gr 1	active	6/12ph 6/9	nil	fl. and dem.	6/12ph6/9	nil	fl and dem	nil
Arun	40	M	pmb c	N	6/36ph6/24	6/18ph6/12	gr2	1 dd	13	12	T.Azithro	6/24nip	gr 2	active	6/24nip	gr 2	active	6/24nip	gr 2	active	nil
Tamilselvan	15	M	o m c	va c	6/36p	6/18ph6/12	gr 1	1.5 dd	16	12	T.Azithro	6/18ph6/12	gr 1	active	6/12ph6/9	nil	fl. and dem.	6/12ph6/9	nil	fl and dem	nil
Rathikala	26	F	c e	o m c	6/24ph6/18	6/60p	gr 3	1.5 dd	11	11	T.Azithro	6/24pH6/18	gr 2	active	6/18ph6/12	gr 2	active	6/12nip	nil	fl and dem	nil
Arumugam	45	M	N	jpc	6/6	6/24ph6/18	gr 1	1 dd	13	11	T.Azithro	6/18nip	gr 1	active	6/12 nip	nil	fl. and dem.	6/12nip	nil	fl and dem	nil
Muniammal	40	F	N	va c	6/12ph6/6	6/12ph6/9	gr 1	1 dd	18	14	T.Azithro	6/12ph6/9	gr 1	active	6/9ph6/6	nil	fl. and dem.	6/9ph6/6	nil	fl and dem	nil
Abdul. R	45	M	N	c e	6/6p	6/24ph6/18	gr 1	1.5 dd	12	13	T.Azithro	6/24ph6/12	gr 1	active	6/12nip	nil	fl. and dem.	6/12nip	nil	fl and dem	nil
Ramesh	23	M	N	m c	6/9ph6/6p	5/60nip	gr 3	2 dd	11	13	T.Azithro	5/60nip	gr 2	active	6/36nip	gr 2	active	6/36nip	gr 2	active	nil
Ravi	36	M	N	m c	6/6p	6/36nip	gr 2	2 dd	14	13	T.Azithro	6/36ph6/24	gr 2	active	6/24ph6/18	gr 1	active	6/24ph6/18	nil	fl and dem	nil
Pushpa	45	F	j p c	N	6/24nip	6/9ph6/6	gr 2	1 dd	13	15	T.Azithro	6/24nip	gr 2	active	6/24ph6/18p	nil	fl. and dem.	6/12nip	nil	fl and dem	nil
Pavitra	15	F	m c	N	4/60nip	6/6	gr 2	2.5dd	16	12	T.Azithro	5/60nip	gr 2	active	6/36nip	gr 2	active	6/36nip	nil	fl and dem	nil
C.Ravi	48	M	o m c	m c	6/36nip	4/60p	gr 3	1.5 dd	14	17	T.Azithro	5/60nip	gr 3	active	6/60ph6/36	gr 3	active	6/60ph6/36	nil	fl and dem	nil
Munni	40	F	N	pmb c	6/6p	6/24ph6/18	gr 1	1.5 dd	12	12	T.Azithro	6/18ph6/12	gr 1	active	6/12nip	nil	fl. and dem.	6/12nip	nil	fl and dem	nil
Rubavathy	30	F	va c	N	6/18nip	6/12ph6/9	gr 2	2 dd	13	12	T.Azithro	6/18PH6/12	gr 2	active	6/18nip	gr 1	active	6/18nip	gr 1	active	nil
Gobi	33	M	m c	N	2/60nip	6/6	gr 3	2 dd	12	12	T.Azithro	3/60nip	gr 3	active	3/60nip	gr 3	active	4/60ph5/60	gr 1	active	nil
Yuvaraj	17	M	mult. C	N	6/24ph6/18	6/6	gr 1	1-1.5 dd	14	12	T.Azithro	6/18ph6/12	gr 1	active	6/18ph6/12p	nil	fl. and dem.	6/18ph6/12	nil	fl and dem	nil
Malar	29	F	m c	N	6/36nip	6/9p	gr 2	1.5 dd	12	12	T.Azithro	6/36nip	gr 2	active	6/36ph6/24	gr 1	active	6/36ph6/24	nil	fl and dem	nil
Bhoopalan	20	M	m c	N	6/60nip	6/12ph6/9	gr 2	1 dd	14	14	T.Azithro	6/60nip	gr 2	active	6/36nip	gr 1	active	6/36nip	nil	fl and dem	nil
Sensaiya	18	M	o m c	m c	6/36p	6/60nip	gr 3	2 dd	13	13	T.Azithro	6/60PH6/36	gr 2	active	6/60ph6/36	gr 2	active	6/36nip	nil	fl and dem	nil
Geetha	17	F	o c	m c	6/6p	6/36nip	gr 2	1 dd	13	15	T.Azithro	6/36nip	gr 2	active	6/24nip	gr 2	active	6/24nip	nil	fl and dem	nil
Akash	14	M	N	va c	6/18ph6/9	6/12ph6/9	gr 1	1 dd	15	16	T.Azithro	6/12ph6/9	gr 1	active	6/12ph6/6	nil	fl. and dem.	6/12ph6/6	nil	fl and dem	nil
Narayanswamy	33	M	m c	N	4/60nip	6/6	gr 3	1.5 dd	11	12	T.Azithro	4/60nip	gr 2	active	6/60pnip	gr 2	active		gr 1	active	nil