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Review Article

Uveitis Disease: Inflammation of Uvea

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ABSTRACT

Uveitis is a complex multifactorial autoimmune disease. The four anatomical types of uveitis include anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis. Most of the uveitic entities are idiopathic. The disease is more common in males with mean age group of 35 to 45 years. Advanced diagnostic tests like molecular biologic study of intraocular fluid in infectious uveitis and high-resolution CT chest imaging techniques have contributed to etiological diagnosis of uveitis. The disease can cause varying degrees of visual loss. In the US, uveitis has been identified as a cause for 10% of the legal blindness. Although exact visual morbidity due to uveitis in India is unknown, it appears to be relatively more when compared to developed countries. HLA-B27 anterior uveitis accounts for 50% of acute anterior uveitis. Intermediate uveitis is mostly idiopathic. Posterior uveitis can be infectious or non-infectious.

Keyword: Uveitis Disease, Inflammation of uvea, Types of uveitis, Path physiology, Diagnosis, Treatment, Prognosis, Epidemiology.

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INTRODUCTION OF UVEITIS

Uveitis is the inflammation of the uvea, the pigmented layer that lies between the inner retina and the outer fibrous layer composed of the sclera and cornea. The uvea consists of the middle layer of pigmented vascular structures of the eye and includes the iris, ciliary body, and choroid. Uveitis is an ophthalmic emergency and requires a thorough examination by an optometrist or ophthalmologist and urgent treatment to control the inflammation.

CLASSIFICATION

Uveitis is classified anatomically into 4 Types:
1) Anterior.
2) Intermediate.
3) Posterior.
4) Panuveitic forms.
Based on the part of the eye primarily affected.[1] Prior to the twentieth century, uveitis was typically referred to in English as "ophthalmia."[2]

Anterior uveitis: Includes iridocyclitis and iritis. Iritis is the inflammation of the anterior chamber and iris. Iridocyclitis presents the same symptoms as iritis, but also includes inflammation in the ciliary body.[3] Anywhere from two-thirds to 90% of uveitis cases are anterior in location. This condition can occur as a single episode and subside with proper treatment or may take on a recurrent or chronic nature. (Fig.2)

Intermediate uveitis: Also known as pars planitis, consists of vitritis-which is inflammation of cells in the vitreous cavity, sometimes with snow banking, or deposition of inflammatory material on the pars plana. There are also "snowballs," which are inflammatory cells in the vitreous.

Posterior uveitis: Chorio retinitis is the inflammation of the retina and choroid.

Pan-uveitis: Is the inflammation of all layers of the uvea.

SYMPTOMS AND SIGNS

Anterior uveitis: (Fig.3) Burning of the eye, Redness of the eye, Blurred vision, Photophobia or sensitivity to light, Irregular pupil, Eye pain. Floaters, which are dark spots that float in the visual field, Headaches, Synechia.

Intermediate uveitis: (Fig.4) Most common are Floaters and Blurred vision. Intermediate uveitis normally only affects one eye. Less common is the presence of pain and photophobia.[5]

Posterior uveitis: (Fig.5) Inflammation in the back of the eye is commonly characterized by Floaters, Blurred vision, Photopsia or seeing flashing lights.

CAUSES:

All of the widely [6] administered vaccines have been reported to cause uveitis. Uveitis is usually an isolated illness, but can be associated with many other medical conditions.

Noninfectious or Autoimmune Causes: Behcet disease, Crohn's disease, HLA-B27related uveitis, Sarcoidosis, Spondyloarthritis, Sympathetic ophthalmia, Tubulointerstitial nephritis and uveitis syndrome.

Infectious causes: Uveitis may be an immune response to fight an infection inside the eye. While representing the minority of patients with uveitis, such possible infections include; Brucellosis, Leptospirosis, Lyme Disease, Presumed Ocular Histoplasmosis Syndrome, Syphilis, Toxocariasis, Toxoplasmic chorio retinitis, Tuberculosis, Zika Fever.[10]

Associated with systemic diseases:
Systemic disorders that can be associated with uveitis include:[11][12] Ankylosing Spondylitis, Behçet's Disease, Chronic Granulomatous Disease, Enthesitis, Inflammatory Bowel Disease, Kawasaki's Disease, Multiple Sclerosis, Reactive Arthritis, Sarcoidosis, Whipple's Disease.

Drug related side effects: Rifabutin, a derivative of Rifampin has been shown to cause uveitis.[12] Several reports suggest the use of quinolones especially Moxifloxacin may lead to uveitis.[13] All of the widely [14] administered vaccines have been reported to cause uveitis.

White Dot syndromes: Occasionally, uveitis is not associated with a systemic condition: the inflammation is confined to the eye and has unknown etiology. In some of these cases, the presentation in the eye is characteristic of a described syndrome, which is called white dot syndromes, and include the following diagnoses; Acute Posterior Multifocal Placoid Pigment Epitheliopathy, Birdshot Chorioretinopathy, Multifocal Choroiditis And Panuveitis, Multiple Evanescent White Dot Syndrome, Punctate Inner Choroiditis, Serpiginous Choroiditis.

Masquerade syndromes:
Masquerade syndromes are those conditions that include the presence of intraocular cells but are not due to immune-mediated uveitis entities. These may be divided into neoplastic and nonneoplastic conditions.

Non-neoplastic: Retinitis Pigmentosa, Intraocular Foreign Body, Juvenile Xanthogranuloma, Retinal Detachment.

Neoplastic: Retinoblastoma, Lymphoma, Malignant Melanoma, Leukemia, Reticulum Cell Sarcoma.

PATHOPHYSIOLOGY

Immunologic factors: Onset of uveitis can broadly be described as a failure of the ocular immune system and the disease results from inflammation and tissue destruction. Uveitis is driven by the Th17T cell subpopulation that bear T-cell receptors specific for proteins found in the eye.[15] These are often not deleted centrally whether due to ocular antigen not being presented in the thymus (therefore not negatively selected) or a state of energy is induced to prevent self targeting.[16][17] Autoreactive T cells must normally be held in check by the suppressive environment produced by microglia and dendritic cells in the eye.[18] These cells produce large amounts of TGF beta and other suppressive cytokines, including IL-10, to prevent damage to the eye by reducing inflammation and causing T cells to differentiate to inducible T reg cells. Innate immune stimulation by bacteria and cellular stress is normally suppressed by myeloid suppression while inducible Tregcells prevention and clonal expansion of the auto reactive Th1 and Th17 cells that possess potential to cause damage to the eye.

Whether through infection or other causes, this balance can be upset and autoreactive T cells allowed to proliferate and migrate to the eye. Upon entry to the eye, these cells may be returned to an inducible Treg state by the presence of IL-10 and TGF-beta from microglia. Failure of this mechanism leads to neutrophil and other leukocyte recruitment from the peripheral blood through IL-17 section. Tissue destruction is mediated by non-specific macrophage activation and the resulting cytokine cascades.[19] Serum TNF-α is significantly elevated in cases while IL6 and IL-8 are present in significantly higher quantities in the aqueous humour in patients with both quiescent and active uveitis.[20] These are inflammatory markers that non-specifically activate local macrophages causing tissue damage.

Genetic Factors: The cause of non-infectious uveitis is unknown but there are some strong genetic factors that predispose disease onset including HLA-B27[21][22] and the PTPN22 genotype.[23]

Infectious agents: Recent evidence has pointed to reactivation of herpes simplex, varicella zoster and other viruses as important causes of developing what was previously described as idiopathic anterior uveitis. Bacterial infection is another significant contributing factor in developing uveitis.

DIAGNOSIS

Diagnosis includes dilated fundus examination to rule out posterior uveitis, which presents with white spots across the retina along with retinitis and vasculitis. Laboratory testing is usually used to diagnose specific underlying diseases, including rheumatologic tests (e.g. antinuclear antibody, rheumatoid factor, angiotensin converting enzyme inhibitor) and serology for infectious diseases (Syphilis, Toxoplasmosis, Tuberculosis). Major histocompatibility antigen testing may be performed to investigate genetic susceptibility to uveitis. The most common antigens include HLA-B27, HLA-A29 (in birdshot chorioretinopathy) and HLA-B51 (in Behçet disease). (Fig.6) Radiology X-ray may be used to show coexisting arthritis and chest X-ray may be helpful in sarcoidosis.

TREATMENT

What should treatment achieve?

1. Relieve pain and discomfort.
2. Prevent sight loss due to the disease or its complications.
3. Treat the cause of the disease where possible, that is, treat the inflammation.

The above 3 different aims of treatment explains the wide variety of drugs used in treating uveitis. In a few types of uveitis, the inflammation is caused by an infection and so patients are treated with antibiotics or antiviral drugs.
Apart from this situation, the drugs used to treat uveitis fall into 3 main groups.

Steroids: Apart from certain types of uveitis caused by infections, the majority of cases are treated by altering the activity of the immune system. The immune system has recognised a part of our own body as foreign and reacts against it. This reaction is called inflammation. The action desired by those treating uveitis is to suppress the immune system or to "turn it down". Steroids have wide ranging effects but their action may be looked on as being anti-inflammatory and immunosuppressant". Steroids make up the major part of uveitis treatment.
They are used in different forms:

- Eye drops
- Peri -ocular injections. (injections locally around the eye).
- Systemically, via the blood stream, either by oral (tablets) or intra-venous infusion (drip).

The method used to "deliver" the steroid depends on the severity of the uveitis and where, in the eye, the inflammations.

Eye Drops: Steroid drops are used for Anterior Uveitis (iritis or iridocyclitis). The drops can penetrate the part of the eye in front of the lens, where anterior uveitis occurs. There are many different names of drops and for that reason a list of different drops is not included here. Basically the drops will differ in their strength. The frequency of taking the drops will also vary depending on the severity of the uveitis. In a very severe case, the strongest drop may be used every hour initially, whereas someone else with a mild

inflammation may only need to use the weakest drop once or twice a day. Anterior uveitis, remember, may be acute,(coming on suddenly and stopping in weeks) or chronic (coming on slowly and lasting for months or years).

Periocular Injections: Sometimes it is considered necessary to use injections around the eye to deliver the steroid treatment. There are only certain situations where injections offer a better way forward than either tablets or drops. They are usually used along with other forms of treatment. Situations where injections are used include:

- Severe cases of Anterior uveitis which can not be controlled by drops alone.
- Intermediate uveitis
- To avoid or limit systemic steroids in the younger age groups.

This is to avoid the side effects of systemic steroids which are more significant in children. From the patient's point of view it is fairly obvious what the drawback of the injection is. If given a choice between taking the same drug by drop, tablet or injection, you wouldn't need a questionnaire to find out that the injection wouldn't get many votes. Injections, as stated before, are only considered in certain situations when they are thought necessary. Injections may have distinct advantages over other means in some situations. Injections do vary in type and the discomfort of the injection itself and its aftereffects will vary. Usually they are straight forward and not too uncomfortable. If our doctor thinks that injections would be necessary, then we mustn't be afraid of asking what is involved. This is particularly the case with children where the use of a general anesthetic is sometimes considered.

Systemic Steroids: Oral Steroids - Prednisolone is the name given to the tablets likely to be used. The use of systemic steroids is more serious than, say, steroid drops because in this form there are potentially significant side effects. It becomes even more important to be able to talk to our doctors about the benefits and the risks of the treatment..There are many different situations in which oral steroids are considered. So far we have seen how Anterior uveitis is usually treated by drops alone. In certain circumstances, then injections may be used. If Anterior uveitis is particularly severe or resistant to treatment with drops and/or injections then itis possible that systemic steroids may be considered. However, the main use of oral steroids is to treat those types of uveitis that affect the back of the eye, (posterior uveitis, retino choroiditis and pan uveitis are examples of several terms used).

Dosage: Prednisolone is usually found as 1milligram (mg.) and 5mg. tablets. The dosage usually starts off very high and then the inflammation is observed very closely and when it is being controlled the dosage will be gradually tapered off to the lowest possible dose which will keep the inflammation from recurring. It will come as no surprise that there are no typical dosages or times for the tapering off period! As we know by now there are so many different types of uveitis, there may be one or both eyes involved, the uveitis may be severe of mild and so on. However the range of high dosage would be considered to be40-80mg. At the other end, if the steroid can not be discontinued altogether then it is thought that dosages of 7.5 mg and below give rise to "acceptable" risks of side effects. If the uveitis seems to be resistant to the steroid therapy or if the inflammation starts up again when the steroids drop below, say, 40mgs. then other immunosuppressant's may be used along side the steroids.

Intra-venous Steroids: Occasionally, a situation may arise when rapid control of an acute episode of inflammation is needed. This may be if the sight is threatened and a high dosage of steroid needs to be delivered quickly. In this case a steroid called methyl prednisolone may be used. It is given by means of an intravenous infusion (a drip) . The dose is infused over approx.2 hours and is usually repeated 24 hours later for up to 3 doses. This procedure is normally carried out in a hospital ward because close monitoring of side effects and reactions eg blood pressure are required. rapid effect hopefully follows so that a routine of oral drug treatment can be resumed.

Side Effects of Steroids: large separate article, or even a book, could easily be written about the side effects of steroids We must be careful when we think about this. On one hand, there can be serious side effects which can be troublesome and have to be appreciated when balancing benefit and risk of treatment. On the other hand, most of us who take steroids will only experience a few, if any, significant side effects. So we must respect the list of possible problems caused by taking steroids, but we mustn't panic when we see the "long list".

The side effects of systemic steroids: Nausea, dyspepsia (heartburn), Increased appetite, weight gain and fluid retention, Mood changes, including depression or euphoria. Hypertension, (high blood pressure), Increased hair growth, Diabetes, Osteoporosis, Bruising and delayed wound healing, Growth suppression in children, Cataract, Glaucoma (raised eye pressure).

Immunosuppressants: Steroids do suppress the immune system in a general way, but there are a different group of drugs that may be used to treat some forms of uveitis, in certain situations. These drugs tend to target the immune system more precisely than steroids. They are usually used in conjunction with

steroids. All these drugs have their share of side effects.

The main examples are:

- Cyclosporine.
- Azathioprine know as Imuran.
- Methotrexate.
- Mycophenolate mofetil often know as cellcept.
- Tacrolimus, also knows as Prograf 500.

Mydriatics: Mydriatics are used in the treatment of anterior uveitis and have 2 main aims:-

- To relieve pain and light sensitivity.
- To prevent sight threatening complications.

Mydriatic eye drops, such as atropine and cyclopentolate, are used. Again there are many names of these type of drops, but they are grouped into "long" or "short" acting. They may be used for variable lengths of time depending on individual cases. A mydriatic works by "paralyzing" the muscles of the iris and the ciliary body. (it is the movement of these inflamed muscles that causes the pain). When these drops have taken their effect the pupils will be dilated. This may cause blurring of the vision. The mydriatics are also useful because they help prevent complication which may occur in anterior uveitis where the inflamed iris "sticks" to the lens. This is known as adhesions or synechiae. This can lead to a raised pressure in the eye which may be sight threatening if not treated. The use of mydriatics is simple but the blurring of near vision, for a while after they are put in, can be disruptive for some patients at work or at home. It is important, then, to remember that these drops are not just relieving pain and discomfort but they can be very important in preventing significant complications later on.

NATURAL PRODUCT USED IN UVEITIS:

- **Turmeric:**
- **Turmeric Benefits for Uveitis:**

From 2010, many studies have been launched on the use of turmeric in treating eye ailments like uveitis. Turmeric has powerful antioxidant properties that can both protect and boost the functioning of the immune system. Studies demonstrate that turmeric could help in the reduction of chronic uveitis symptoms. Here are key findings of some of the research studies which have found that turmeric can prove beneficial for uveitis. A study was conducted on a curcumin phosphatidylcholine compound called Meriva (specifically Norflo tablets) on treating chronic anterior uveitis. The compound was given twice daily to patients with differing etiologies of this condition. There were 106 patients studied over a 12 month period. They were divided into 3 groups – autoimmune uveitis, herpetic uveitis and different uveitis etiologies. (Fig.7)

The results found that all patients tolerated Meriva well. It reduced eye discomfort in around 80% of patients after a few weeks. The conclusion was the curcumin based medications could benefit those with anterior uveitis and other eye degenerative and inflammatory conditions such as glaucoma, dry eye, diabetic retinopathy and maculopathy. Meriva formulation is well tolerated up to 2 tablets a day even for long term use. It is suggested that while more research is required, curcumin is a potent immuno-modulating agent and anti-inflammatory and hence can have a great effect on inflammatory cascade. In another small study of 36 uveitis patients divided into 2 groups, the group taking the turmeric tablets showed greater improvement and no side effects compared to the group that was given corticosteroid therapy.

In one study, 32 patients with chronic anterior uveitis were given 375mg turmeric containing curcumin thrice daily for a period of 12 weeks. They were divided into two groups of 18 and 14 patients. The first group got only curcumin. The second group had a severe PPD reaction and was also given anti-tubercular medication. All the curcumin patients showed signs of improvement, whereas only 86% of the second group did so. The recurrence rates of both groups were studied over 3 years. Curcumin seems to offer the same efficacy and recurrences after treatment as corticosteroids without the side effects. A double-blind multi-centric clinical study has been suggested for further validation of the benefits of curcumin.

Dosage: 3600 mg is the daily oral dose of curcumin and this can go up to 8g / day. We can consume 0.5 – 3g/day of powdered turmeric root. In clinical trials, 375mg of curcumin 3 times daily was administered to patients who had chronic anterior uveitis. You also get turmeric as liquid extracts and tinctures. I would strongly recommend to consult a doctor before going ahead and deciding your dose. This is because every case is different and several people may have allergies and other disorders which may get aggravated with use of turmeric.

Precautions: Turmeric included in foods is generally safe. Those who have diabetes or gall bladder problems must avoid turmeric supplements. Taken in excess, it can cause diarrhea or nausea. It could interact with medications for stomach acids and blood thinning medications. Always consult your doctor before taking turmeric or other herbal supplements. Turmeric supplements are contraindicated for pregnant and breastfeeding women. It could have abortion-inducing effects and also cause menstrual bleeding. Rare cases of kidney stones and contact dermatitis have been reported.

MARKETED PREPARATION: (Fig.8)

- ✓ Uvical pills.
- ✓ Curcumin phytosome 500mg caps.

- ✓ Turmeric curcumin 500mg caps.

PROGNOSIS: The prognosis is generally good for those who receive prompt diagnosis and treatment, but serious complication including cataracts, glaucoma, band keratopathy, macular edema and permanent vision loss may result if left untreated. The type of uveitis, as well as its severity, duration, and responsiveness to treatment or any associated illnesses, all factor into the outlook.

EPIDEMIOLOGY: Uveitis affects approximately 1 in 4500 people and is most common between the ages 20 to 60 with men and women affected equally. In western countries, anterior uveitis accounts for between 50% and 90% of uveitis cases. In Asian countries the proportion is between 28% and 50%.[29] Uveitis is estimated to be responsible for approximately 10%-20% of the blindness in the United States.

CONCLUSIONS

Most of the studies conducted so far on this subject are retrospective, with small groups of patients. The most important prognostic factors for cataract surgery in the eyes of pediatric patients with uveitis have been patient selection and control of intraocular inflammation. All eyes that have done well in published reports have been quiet, well-controlled eyes, with no history of recent flare-ups. Chronic uveitis has been associated with severe complications and poor visual outcomes. Sometimes, in uveitic eyes, especially patients with JIA–uveitis, despite the use of maximum immunosuppressive therapy and biologicals along with local or systemic steroids, the ocular inflammation remains active. This is the group of patients who have poor visual recovery, severe inflammatory sequelae, and sight-threatening complications if an IOL is inserted. The existing studies advise against using an IOL in patients with active uveitis despite maximum medication, very young children, hypotony, eyes with rubeosis, indeterminate cause of uveitis, and when IOL-related complications have developed in the other eye. The data advises for minimally invasive small incision cataract surgery with foldable IOL, especially in unilateral cataract, when the uveitis is well controlled and the patient is well controlled systemically, So far, we do not have definite answers. The existing data are not sufficient for us to derive definitive conclusions or recommendations regarding lens implantation in pediatric uveitis patients. Therefore, multiple factors have to be taken into consideration before deciding for or against IOL insertion in pediatric uveitic eyes. There needs to be a prospective and multicenter study involving ophthalmologists and rheumatologists to have some definite answers on this subject. Till then, patients must be evaluated on a case-by-case basis, using extreme caution, before the final decision is made.

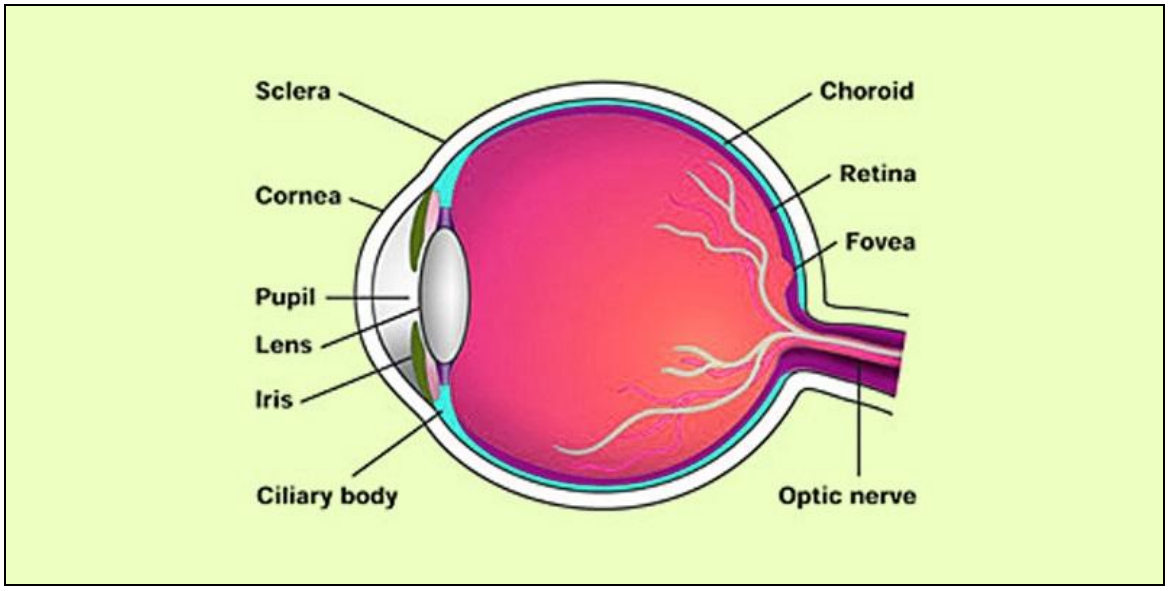

Fig. 1: Eye Structure.

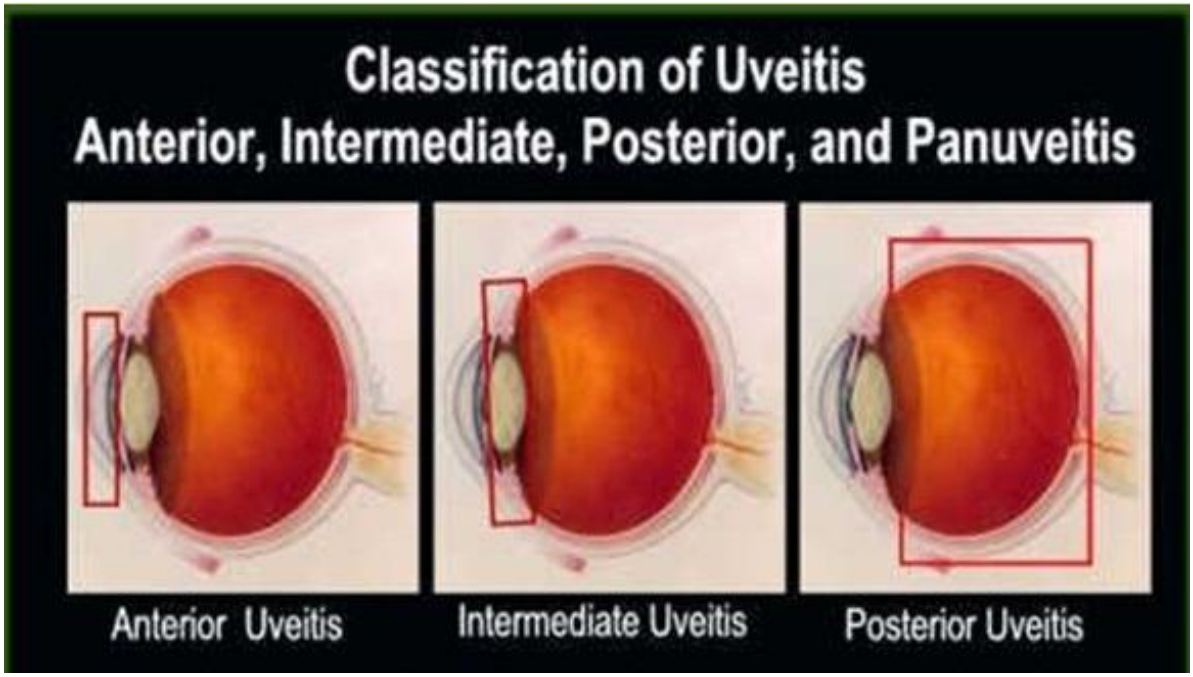

Fig. 2 : Classification of Uveitis

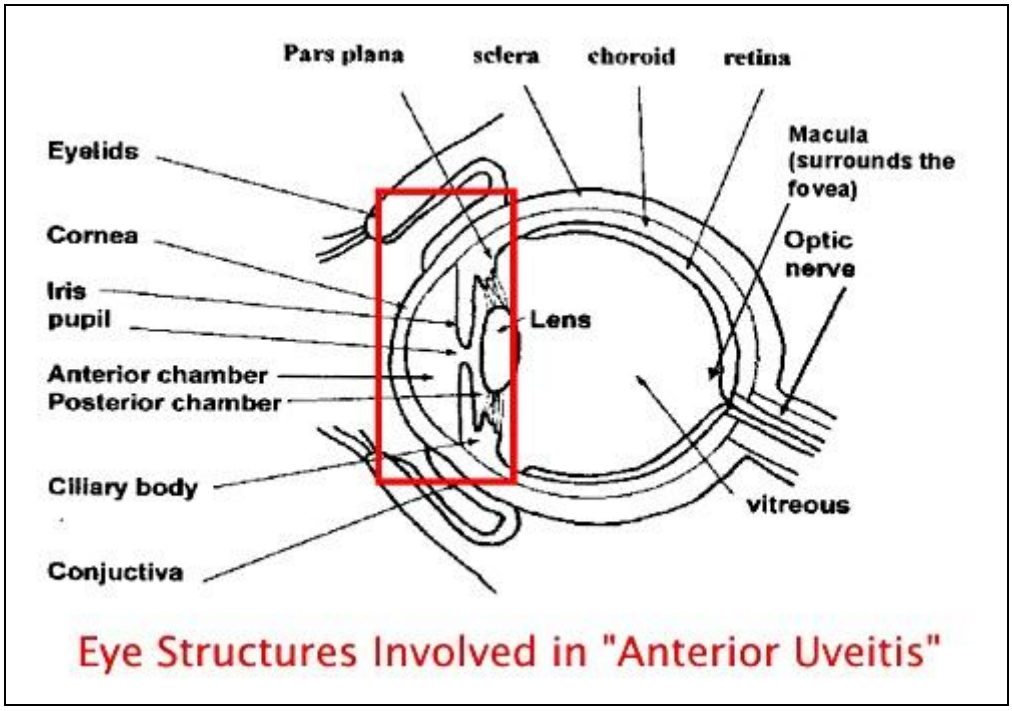

Fig. 3 : Anterior Uveitis

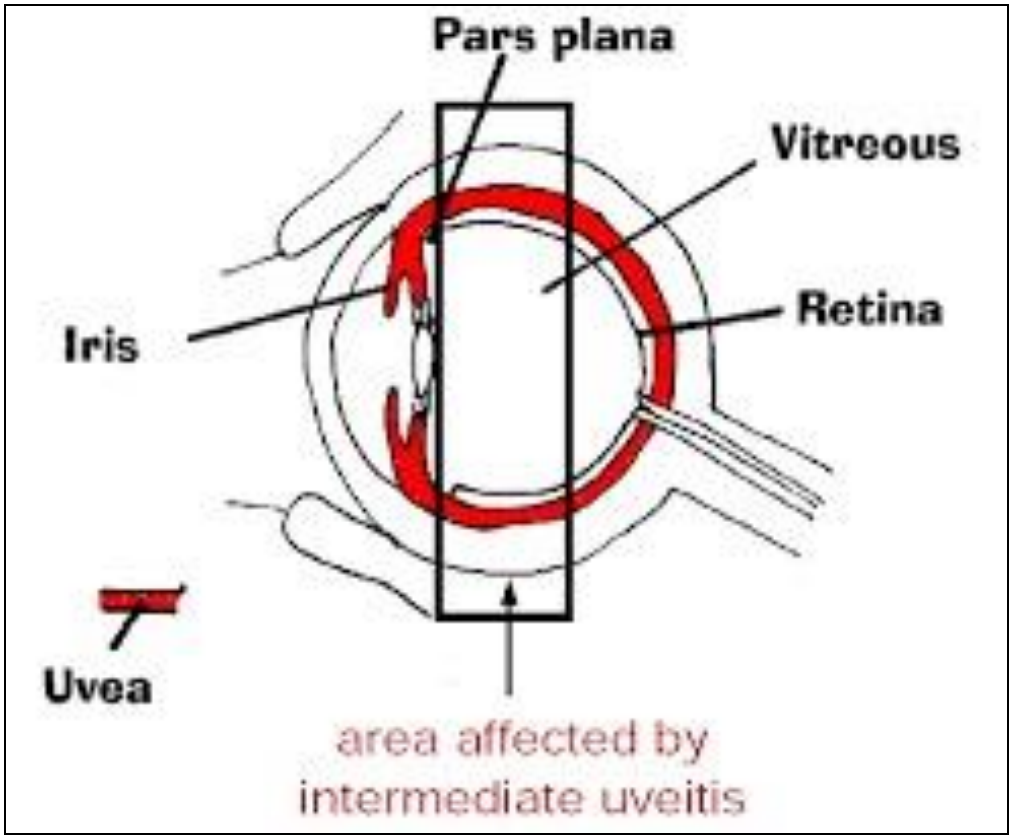

Fig. 4: Intermediate uveitis.

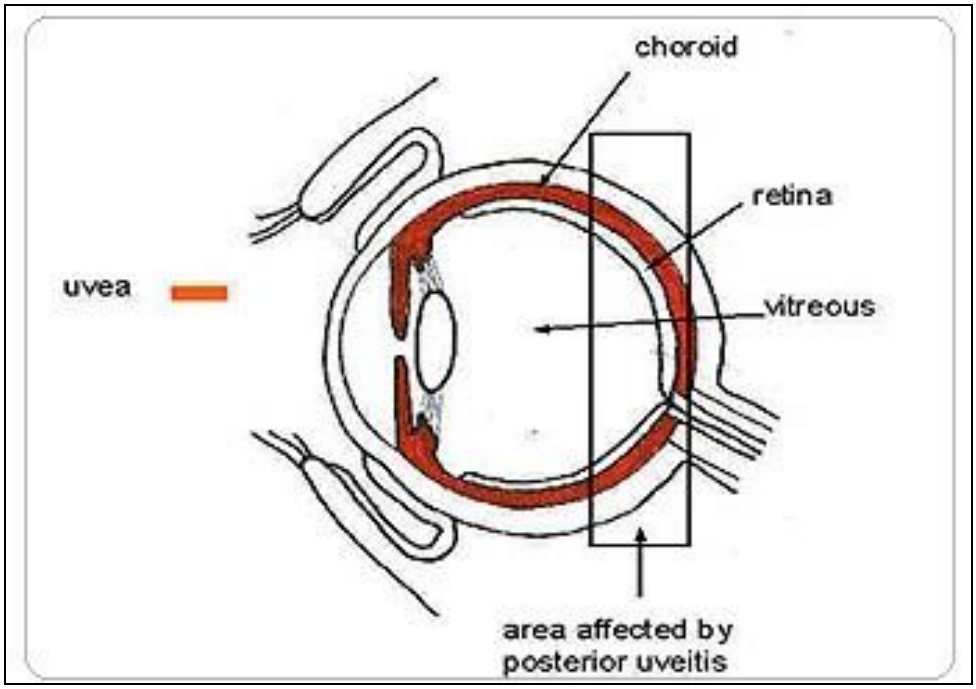

Fig. 5: Posterior uveitis

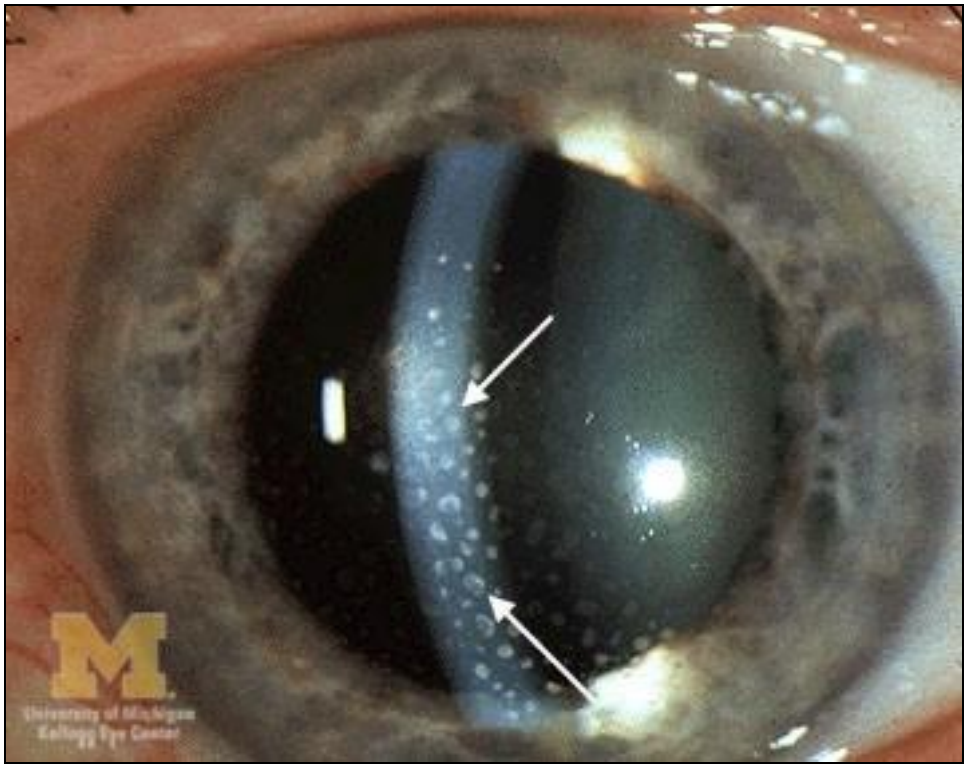

Fig. 6: Keratic precipitates

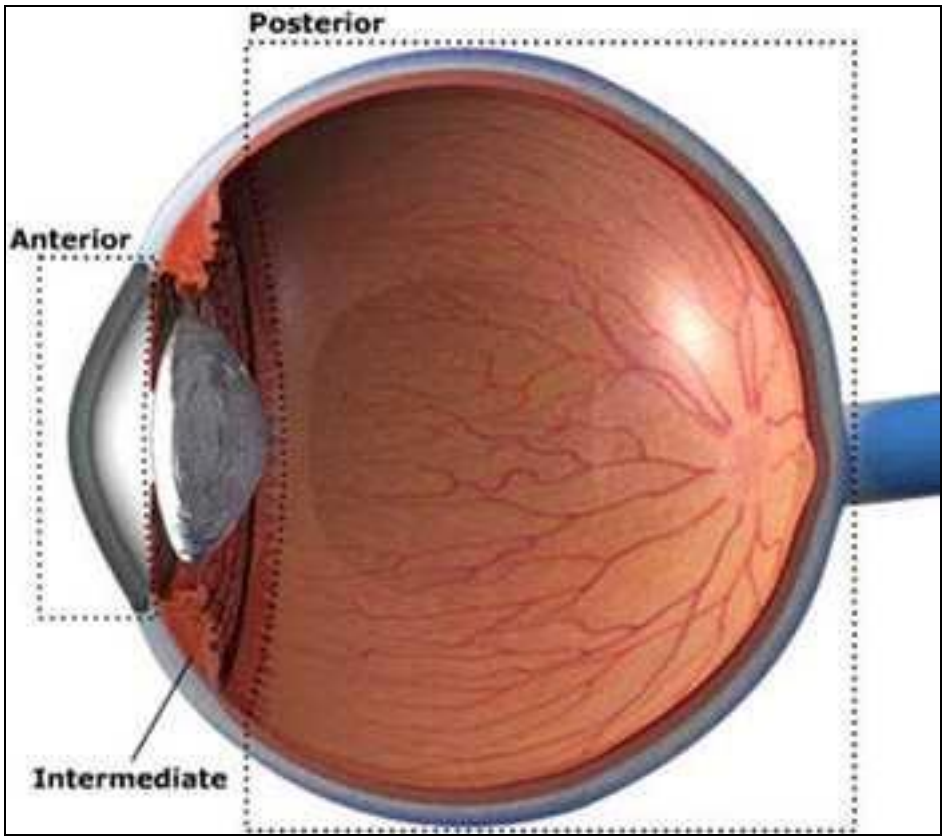

Fig. 7: Effect Of Turmeric On Uveitis

Fig. 8: Marketed Preparation of Turmeric

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