CLINICAL PATTERN OF

RECURRENT HERPES SIMPLEX KERATITIS

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CERTIFICATE

This is to certify that the dissertation entitled " **CLINICAL PATTERN OF RECURRENT HERPES SIMPLEX KERATITIS"** presented herewith by ***Dr. A.V. RAMYA*** to the faculty of Ophthalmology, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.S. degree in Ophthalmology is a bonafide work carried out by her under my direct supervision and guidance.

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DECLARATION

I, Dr.A.V.Ramya, solemnly declare that the dissertation titled **"CLINICAL PATTERN OF RECURENT HERPES SIMPLEX KERATITIS"** has been prepared by me.

This is submitted to **The Tamilnadu Dr.M.G.R.Medical University**, Chennai, in partial fulfillment of the regulations for the award of **MS** degree Branch [Ophthalmology].

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INTRODUCTION

The human herpes virus is an important source of ophthalmic morbidity worldwide. Herpes simplex virus however, continues to be an important cause of unilateral corneal blindness worldwide. It is a multifaceted disease capable of inducing the most baffling problems through both infectious and immune mechanisms. Despite considerable progress in understanding the virus at cellular and molecular levels the prospect of prevention still appears to be a long way off.

VIROLOGY

Herpes simplex virus belongs to a family of viruses called Herpesviridae. They are composed of a central deoxyribo nueclic acid Core and a protein capsid with 162 hollow cylindrical capsomeres. This nucleocapsid is surrounded by an envelope forming a virus particle (virion) with an overall diameter of 130-180nm.

VIRUS TYPES:

There are two types of herpes simplex virus , namely, type 1 and 2. In general, type 1 causes infection above the waist like herpes labialis

and dermatitis and type2, below the waist (Herpes genitalis). Thus the rare neonatal herpes simplex virus infection including herpetic keratitis and conjunctivitis is due to herpes simplex virus type 2 in a majority of cases.

VIRAL STRAINS:

The severity and frequency of ocular disease may be influenced by strain difference. Strains which produce large amount of glycoproteins are capable of inducing more humoral and cell-mediated immune response[16]. These strains may be associated with more severe form of corneal stromal disease. The viral genome may also play a role in determining the clinical response to topical steroids.

PATHOGENESIS

It causes a lytic infection[17] Herpes simplex virus usually affects tissues of ectodermal origin, such as skin, mucous membrane, or the nervous system. After the attachment to specific receptors on the surface of human cell membrane it enters the cells by pinocytosis (penetration). The deoxyribo nueclic acid released into the cells travels to the nucleus. There follows an eclipse period during which no virus can be detected. In fact the viral deoxyribo nueclic acid induces the production of both host and virus-specific enzymes, namely, thymidine kinase and deoxyribo nueclic acid polymerase. Viral proteins synthesised in the cytoplasm are transferred to the nucleus where the nucleocapsid is assembled. The nucleocapsid gains an envelope as they bud through the nuclear membrane. The host cell become packed with such particles before it ultimately undergoes cell lysis and releases the infectious particles.

LATENCY AND REACTIVATION

Like other herpes viruses herpes simplex virus has the ability to induce latent infection. After primary infection, that is the host's first exposure at the peripheral site, the virus enters the sensory nerve

endings which supply the site of peripheral epithelial infection, usually the oropharynx. Virus particles travel centripetally to the neuronal cell body by retrograde axoplasmic flow. Here they can survive for decades probably integrated into the host-cell nuclear deoxyribo nueclic acid yet they leave the cell morphologically, antigenically, and functionally normal.

The virus enters the trigeminal ganglion via any of the 3 major divisions of the fifth nerve. The reactivated virus may travel down by centrifugal axoplasmic flow despite and independent of the original portal of entry to cause peripheral disease.

The cornea itself is a site of persistent infection[12]; therefore injudicious use of topical steroids in chronic disease may promote proliferation and penetration of virus within the cornea. For the same reason considerable care must be taken while selecting patients with corneal opacification for treatment with phototherapeutic keratectomy.

CLINICAL FEATURES

PRIMARY INFECTION

Neonates are protected by maternal antibody for six months. Infection with herpes simplex virus for the first time can develop at any age although most cases occur within the first few years of life. Salivary contamination from a person with silent salivary shedding of herpes labialis is the most common source of infection. Aphthous stomatitis is the usual clinical picture, which can range from subclinical to very severe infection. However primary herpes simplex virus infection can also occur in other mucous membranes, including the conjunctiva.

PRIMARY OCULAR HERPES SIMPLEX VIRUS INFECTION

It most commonly manifests as blepharoconjunctivitis which is predominantly unilateral. The periorbital skin can develop intense blisters associated with conjunctivitis and blepharitis. Extensive spread on the facial skin can occur, particularly in eczematous individuals. Herpetic canaliculitis can lead to punctal stenosis.

The conjunctivitis is usually follicular although severe cases may develop pseudo-membranous reaction. Preauricular lymphadenopathy often accompanies the conjuctival involvement in 30-50% of cases. Some times it is difficult to distinguish acute follicular conjunctivitis caused by herpes simplex virus from that caused by adenovirus. Signs that can be used to distinguish herpes simplex virus keratitis from adenovirus keratitis include the following

- The distinctive dendritic morphology of herpes simplex virus keratitis
- The presence in primary herpes simplex virus of cutaneous vesicles
- The lack of an associated epidemic
- Unilaterality (only 10% of herpes simplex virus keratitis cases are bilateral, whereas the majority of adenovirus keratoconjunctivitis cases have bilateral involvement)

The morphology of the corneal lesions varies from superficial punctate keratitis, microdendrites or frank dendritic ulceration. Stromal

involvement and uveitis is rare occurring in <10% of patients with primary ocular herpes simplex virus.

Diagnosis:

In cases in which a clinical diagnosis cannot be made, laboratory tests (culture or antigen detection) may be helpful. Serological testing is generally of limited value in establishing a diagnosis because over 90% of the adult population shows serological evidence of herpes simplex virus -1 infection. Therefore, a single positive lgG titer is nondiagnostic, whereas a negative result may be helpful in excluding herpes simplex virus -related disease (on a retrospective basis). A minimum fourfold rise in antibody titer and /or the presence of IgM class antibodies may be helpful in making a retrospective diagnosis of primary infection.

RECURRENT INFECTION:

The major factors which dictate the severity of recurrent herpes are;

- Genetic constituent of host
- Immune response of the host
- The viral strain
- Treatment

Superficial corneal lesions (dendritic and geographic ulcers) are associated with the presence of replicating virus while deeper lesions (stromal, uveal) appear to be predominantly due to the immune response.

BLEPHAROCONJUNCTIVITIS:

Eyelid and /or conjunctival involvement may occur in patients with recurrent ocular herpes simplex virus infection. Blepharo conjunctivitis may or may not accompany epithelial keratitis.

CORNEAL EIPTHELIAL DISEASE:

The morphology of the lesions are quite varied. They can appear as

- superficial punctate keratitis
- stellate epithelial lesions
- Dendritic ulcer
- geographic ulcers.

The vast majority of cases of herpes simplex virus keratitis are those, which present with a corneal epithelial lesion, usually a dendritic

ulcer. Such individuals may experience first episode in adulthood. This is due to reactivation of a latent virus from a previously unrecognized primary ocular infection or from a virus, which has reached the ophthalmic neurons in the trigeminal ganglion during primary infection of the oropharynx. It usually occurs as isolated lesion(s) without involvement of conjunctiva and lids. The presenting symptoms include irritation, watering, photophobia, and occasionally, blurring of vision. Cold sores are common in such individuals but are rarely simultaneous.

Ulcers are usually single but may be several. The lesion begins discrete punctate epithelial keratitis, and then coalesce into dendritic shape lesion consisting of swollen opaque epithelial cells. The mechanism for dendrite formation is not known, but is thought to be related to linear spread of virus from cell to cell in a contiguous manner. With further growth of the dendrite the central epithelium is sloughed off and the lesion stains with fluorescein. The marginal infected cells take up rose bengal stain. The linear branches characteristically end in expansions called “terminal bulbs”. The stroma under the ulcer may show a faint haze and there may be evidence of subepithelial infiltrates,

which mirror the shape of corneal dendrites and are termed "ghost dendrites". They serve as marker for recent epithelial keratitis. Corneal sensation is lost in the areas where lesions are present. Repeated attacks may result in generalized corneal anaesthesia. The distribution of corneal hypoesthesia is related to extent, duration, severity and is difficult to detect. It is not a reliable sign of herpetic disease.

Geographic ulcer develops as a result of centrifugal spread of herpes simplex virus towards peripheral cornea. Risk factors for its development include strain of infecting virus, topical or systemic immuno suppressive therapy and HIV infection.

Typical lesions involve the central cornea. Ulcers at the periphery of the cornea may behave differently sometimes masquerading as ulceration due to staphylococcal infection. They appear to be more resistant to treatment and to have more stromal complications[26]. They are also predisposed to chronic tropic ulceration. In a majority of patients healing occurs with minimal stromal scarring. Repeated attacks and severe infections may result in stromal scarring thinning and vascularization.

STROMAL KERATITIS:

Stromal disease may be divided into infection and immune categories according to currently indicated pathogenesis:

- Infectious disease characterized by necrotizing stromal keratitis;
- Antigen antibody-complement-mediated immune disease characterised by viral interstitial keratitis, immune rings or limbal vasculitis;
- Delayed hypersensitivity reaction characterized by disciform edema.

Necrotising stromal keratitis is typically associated with ulceration. It can follow epithelial disease, superficial stromal disease or disciform keratitis, and is believed to be due to active viral replication and intense immune stromal inflammation. It may be generalized or localized. These cases may have to be differentiated from other forms of microbial keratitis and indeed secondary infection with bacteria and fungal can complicate herpes simplex virus stromal keratitis. Secondary complications include hypopyon, uveitis, posterior synechiae, glaucoma, retrocorneal membrane, cataract, and rarely, perforation.

All three forms of herpetic antigen antibody complex-mediated disease are thought to be due to immune complex hypersensitivity. The interstitial keratitis presents clinically as single or multiple patches of dense white necrotic infiltrates. After several weeks of smoldering, deep, dense leashes of vessels often move in.

Immune-mediated stromal keratitis is the most common form of the stromal disease where an antibody response is mounted against the viral antigen present in the stroma expressed as a result of persistent infection. There is deposition of antigen-antibody-complement in the stroma. Animal studies show additional mechanisms involved in the stromal tissue destruction. It is proposed that CD4+T cells play a significant role in the recognition of antigens presented by Langerhan's cells, which migrate from limbus to central cornea after herpes simplex virus type 1 infection. The activated CD4+T cells release cytokines, in particular interleukin 2 and gamma interferon. Both factors attract large numbers of polymorphonuclear leucocytes, which are responsible for corneal tissue destruction.

Another distinct form of stromal infiltrate is the immune ring of wessely. This represents a circular deposit of antigen-antibody complexes with polymorphonuclear leucocyte infiltrate as a result of complement activation.

Traditionally disciform keratitis has been described under stromal keratitis. However the recent trend is to describe it under endothelitis as the actual mechanism involved is thought to be endothelial cell infection by herpes simplex virus and associated inflammation.

INDOLENT ULCERATION:

Development of persistent epithelial defects or recurrent epithelial erosions can be seen with herpes simplex virus epithelial infection. These are generally round or ovoid ulcers with a grey and thickened margin, which is due to piled up epithelial cells.

The mechanism appears to be due to damage to underlying basement membrane at the time of epithelial infection and denervation. Consequently the epithelium fails to adhere to the basement membrane resulting in persistent defect or recurrent erosion. Additional factors like

lack of trophic innervations, drug toxicity and stromal inflammation may play a role. Viral cultures are negative and the base of the ulcer stains with both rose bengal and fluorescein. Persistent ulcers have the potential to progress to corneal melt, perforation and superinfection.

Indolent ulcers (sometimes referred to as "metaherpetic") have to be differentiated from geographic ulcers, which are characteristically caused by inappropriate steroid use. The latter have flat edges and stain with rose bengal stain. They also change shape due to continued viral progression. Viral cultures will be positive.

HERPES SIMPLEX VIRUS ENDOTHELIITIS:

Progressive or nonprogressive forms of endothelial inflammation can occur with type 1 herpes simplex virus infection. Dendritic ulceration can precede these lesions in some patients. Disciform keratitis is the most common form in which a disc-shaped area of stromal edema occurs without infiltration or vascularization. The area of involvement may be diffuse and central or eccentric. The presenting symptoms include watering, photophobia, discomfort or blurred vision. A history

of herpetic eye disease is usually present. The involved cornea shows appreciable thickening of all layers sometimes with epithelial edema and often with folds in Descements membrane. Careful examination usually reveals keratic precipitates (Kps) in the affected area associated with mild anterior chamber activity. Spontaneous clearing can follow although progression to necrotizing keratitis, vascularization, scarring and thinning is also possible. Delayed hypersensitivity mediated by T lymphocytes is probably important in the pathogenesis of disciform keratitis. The distribution of KPs strictly confined to the endothelium behind the swollen area suggests cell-mediated reaction directed at herpes simplex virus determinants on the surface of endothelial cells[43].

Rarely linear involvement of the endothelium can occur. In these cases stromal edema is seen associated with KPs separating the involved and uninvolved cornea similar to the Khodhadoust line of corneal graft rejection. Slitlamp examination may show dark areas in the endothelium which appear as nonreflective black endothelial areas under a specular microscope. There may be progression of the endothelial line and the associated stromal edema. Immunological studies on the aqueous

aspirates have revealed herpes simplex virus antigen in several of these cases.

HERPES SIMPLEX VIRUS IRIDOCYCLITIS:

All deeper forms of herpes simplex keratitis can be associated with uveitis. However recurrent nongranulomatous anterior uveitis may be an isolated manifestation of herpes simplex virus ocular involvement. Immunological reaction was thought to be the cause in most of the cases although in some cases live viruses have been demonstrated in the anterior chamber and iris tissue[33].

Clinically the severity can vary from mild to severe inflammation which may result in fibrin formation, hypopyon, hyphema, posterior synechiae, segmental iris necrosis similar to the picture seen in zoster keratouveitis, and inflammatory membrane in the angle of the anterior chamber with secondary glaucoma.

TRABECULITIS:

Herpetic peripheral corneal involvement may extend to the trabecular meshwork resulting in trabeculitis. The resultant secondary glaucoma may be transient or lead to permanent damage.

AIDS AND HERPES SIMPLEX KERATITIS :

The experience of herpes simplex keratitis in post-transplant immuno suppressed patients suggests that the condition may be more common and more serious than in immuno competent individuals. It is not as typical as in immuno competent patients. In HIV patients there is a predilection for peripheral as opposed to corneal involvement. More frequent recurrence and prolonged clinical course requiring 2-4weeks of antiviral therapy. If it is assumed that after a first episode a site of chronic latent infection is established in the cornea this suggests, the immuno suppression by HIV infection may impair those mechanisms which are normally responsible for containing such an infection in the cornea[42].

COMPLICATIONS OF HERPETIC EYE DISEASE

Epithelial complications:

- Diffuse punctate or vortex epitheliopathy due to topical antiviral toxicity.
- Recurrent epithelial erosions due to trauma to the basement membrane
- Non healing trophic epithelial defects due to corneal anesthesia may develop which will lead on to trophic ulcers.
- Corneal stromal thinning and perforation rarely due to nonhealing trophic epithelial defects.

Stromal Complications:

- Corneal Stromal scarring leading to surface irregularity
- Irregular astigmatism which may be corrected by carefully fitted gas-permeable hard contact lens, but this might induce recurrence of herpetic keratitis
- Stromal opacification may diminish gradually
- Lipid Keratopathy in patients with corneal stromal vascularization.

TRIGGER FACTORS FOR REACTIVATION[10]

- Deficient immune competence
- Intracellular messenger system
- Physical or emotional stress
- Immuno compromised state
- Fever
- Cold wind
- Systemic illness
- Surgery
- Menstruation
- Trigeminal root ganglion section
- Immuno suppression
- Local trauma, laser glaucoma surgery, refractive surgery

LABORATORY DIAGONSIS

Laboratory tests are not an absolute requisite for the diagnosis of herpes simplex virus infection as clinical features are often highly characteristic (central location, rose Bengal staining pattern and terminal bulbs). However, we believe whenever possible culture should be undertaken to establish a firm diagnosis. The chronic nature of the condition is such that a positive diagnosis once established, is invaluable in guiding management over what may be many years.

The available methods include virus culture, immunological tests, and histopathological examination of keratoplasty specimens.

Tzanck technique, staining of epithelial scrapings taken from the skin or corneal ulcers. Microscopic examination of the Giemsa-stained smear may, but does not invariably reveal typical eosinophilic viral inclusion bodies of Lipschutz in the nuclei. Other stains used are Wrights, hematoxylin-eosin, Papanicolauou's methylene blue and Paragon multiple. The epithelial cells themselves show ballooning

degeneration and a monocytic white cell infiltrate characteristic of viral infection is always present.

The definitive methods of diagnostic testing is isolating virus in tissue culture. The lesion is swabbed and placed in viral transport medium and sent to the laboratory. It is then inoculated on to cell monolayers and incubated at 37°c. A typical cytopathic effect is generally noticed in 2-4 days.

Additional more sophisticated, sensitive and selective tests require more complicated technology and equipment. These tests are worthwhile however in cases where the diagnosis remain in doubt. They include immuno morphological evaluation of scrapings from vesicles, for example immuno fluorescent electron microscopy, immuno peroxidase staining, radioimmunoassay, agar gel immuno diffusion and deoxyribo nueclic acid probes. Serological evaluation tests include fluorescent antibody staining of membrane antigen, immune adherence hemagglutination assay, enzyme –linked immunosorbent assay (ELISA), complement fixation, and neutralization tests. Of the above, the most

readily available and extremely sensitive test is the commercially marketed HERPCHEK which is based on the ELISA system.

Histopathological examination of keratectomy specimens may show granulomatous reaction in deep stroma and around Descemet's membrane. Immunocytochemistry may demonstrate herpes simplex virus antigens in stromal keratocytes, endothelial cells and epitheloid cells. These are more often seen with the necrotising type of herpetic stromal keratitis.

MEDICAL MANAGEMENT

ANTIVIRAL AGENTS

The following topical agents are currently available for use in herpes simplex keratitis. Idoxyuridine, a thymidine analogue was the first agent found to be effective in the treatment of herpes simplex virus keratitis. It is incorporated into the viral deoxyribo nueclic acid, produces faulty deoxyribo nueclic acid chain and also inhibits viral enzyme. It also incorporates into normal host cells which accounts for its toxicity[9]. Available as Iodoxyuridine 0.01% drops Q2 hours. Though idoxyuridine is useful in treating epithelial infection the problems of toxicity, allergic reaction, clinical viral resistance, poor solubility and penetration, and rapid inactivation have led to the use of other antiviral drugs. Notable ocular side effects include contact dermatitis, punctate keratitis, epithelial opacification, chronic epithelial defects, lacrimal punctal stenosis, follicular conjunctivitis, corneal pannus and teratogenicity in rabbits.

Vidarabine, the second agent developed for human use, inhibits viral deoxyribo nueclic acid polymerase and gets incorporated into both

viral and host deoxyribo nueclic acid. It is equally effective as idoxyuridine in treating epithelial disease[18] and being highly soluble is available only as ointment. Its is given in the dosage of vidarabine 3% ointment 5 times daily for 10-14 days. Although it is much less toxic punctate keratopathy (similar to idoxyuridine toxicity) can be problem with topical use. Its use is generally restricted to viral strains resistant to other antiviral agents.

Trifluridine (Triflurothymidine) is a halogenated pyrimidine inhibiting thymidylate synthetase incorporated into viral deoxyribo nueclic acid impairing transcription and translation. It is more potent than idoxyuridine and Vidarabine in healing dendritic ulcers. Also trifluridine is superior to idoxyuridine in the management of steroid-treated corneal ulcers. Although therapeutic levels of the drug can be achieved in the anterior chamber its role is indetermined. It is given in the dosage of Trifluridine 1% drops 9times daily for 10-14 days. Adverse effects include superficial punctal stenosis, corneal filaments, and contact dermatitis. Viral resistance to trifluridine is rare.

Acyclovir (ACV) is a purine analogue. It is specifically activated by virus induced thymidine kinase which initiates phoshorylation. Subsequently two additional phosphates are added by host-cell kinases to produce an active triphosphate form which is inhibitory to viral deoxyribo nueclic acid polymerase than host-cell polymerase. Thus acyclovir is specific to viral-infected cells with low toxicity. After topical application it achieves therapeutic concentration in the anterior chamber[27]. acyclovir is as equally effective as trifluridine and Vidarabine in treatment of herpes simplex keratitis. acyclovir is less toxic to ocular surface than earlier generation antiviral agents and as such represents a major therapeutic advance. However, mutant virus strains with deficient thymidine kinase continue to replicate; therefore the development of drug-resistant strain may poste a problem. It is given in the dosage of Acyclovir 3% ointment 5times daily 10-14 days. Acyclovir 400mg pill TID for 7-10 days

Famcyclovir is an oral Pencyclovir. It is similar to acyclovir in structure and mechanism of action acting against herpes simplex virus 1, herpes simplex virus 2, herpes zoster virus, ebestine bar virus . It

surpasses acyclovir in gastro intestinal absorption [77% vs 30%]. It is metabolized to Pencyclovir intracellularly [active 20 times as long as acyclovir]. Given in dosage of 250 mg oraly bd for 7-10 days in acute infectious epithelial herpes simplex virus. 125 mg bd for 1 yr to prevent recurrences. It is well tolerated and resolves diseases quickly and effectively as topical antiviral and oral acyclovir

Valacyclovir is a prodrug of acyclovir. It has increased gastro intestinal uptake. It's intracellular hydrolysis & 5 times increased bioavailability. Valacyclovir 1000 mg oraly 3 times/day for 7–10 days = acyclovir 400mg 5 times/day for 7-10days. In immuno compromised patients thrombocytopenic purpura & haemolytic uremic syndrome are reported.

DRUGS UNDER RESEARCH

Bromovinyl Deoxyuridine acts by a mechanism similar to acyclovir . It appears to be effective in the treatment of epithelial herpetic disease. Recently Gancyclovir ophthalmic gel has been shown to be equally effective as acyclovir ointment with the added advantage of increased local tolerance. It acts by competitive inhibition of viral deoxyribo nueclic acid.

It is likely that antiviral therapy will advance rapidly in the next few years with 3-hydroxy –2-phosphonly methoxypropyl cytosine, a nucleotide analogue (Cidofovir) showing promise as a broad – spectrum antiviral agent.

CORTICOSTEROIDS

Use of steroid is recommended in certain types of herpes simplex virus infection of the cornea. Corticosteroids suppress inflammation by interfering with the normal immunological response to various stimuli and are an important management tool[37].

The advantages of use of steroids in ocular herpes are

Significant inhibition of

(1) Cellular infiltration

(2) Release of toxic hydrolytic enzymes

(3) Scar tissue formation

(4) Neovascularization.

On the negative side, steroids

1) Suppress the normal inflammatory responses, which may allow deeper spread of a potentially superficial viral infection
2) Open the cornea to opportunistic bacterial or fungal infection through suppression of the immune defence system
3) Enhance collagenolytic enzyme production by most steroids.
4) Steroid induced glaucoma and cataract.

Their use is restricted to the management of stromal keratitis and herpetic uveitis. Steroids do not appear to increase the risk of acquiring herpes simplex virus infection but certainly promote severity of the disease when present. Infectious crystalline keratopathy is a recognized complication of steroids treatment for herpes simplex keratitis. The major problem with steroids is inappropriate use at the epithelial stage particularly as it may improve the symptoms initially. Over-the-counter treatment is undoubtedly responsible for converting what may have been relatively benign disease into irreversible corneal damage.

The strategy for topical corticosteroid therapy of stromal keratitis should be frequent initial administration (every 1-4 hours) followed by tapering of the dose based on the clinical response. Frequently, there will be a threshold below which the stromal inflammation will flare. Therefore, patients should be tapered to the lowest possible steroid dosage that controls their inflammation.

HERPETIC EYE DISEASE STUDY

- Herpes simplex virus stromal keratitis controlled trial of oral acyclovir
  - Oral acyclovir has no beneficial effect on the time of treatment, resolution of keratitis, speed of resolution or 6 months best corrected visual acuity in stromal keratitis
- Herpes simplex virus stromal keratitis controlled trial of topical corticosteroids
  - Topical corticosteroids reduces the persistence and progression and shortens the duration of stromal keratitis
- Herpes simplex virus epithelial keratitis controlled trial of oral acyclovir
  - Oral acyclovir has no benefit in preventing stromal keratitis and iritis
- Herpes simplex virus iridocyclitis controlled trial of oral acyclovir
  - Oral acyclovir has a beneficial effect in treatment of Herpes simplex virus iridocyclitis
- Long term acyclovir in recurrence of epithelial and stromal keratitis

- Not a great difference in recurrence of blepharitis, epithelial keratitis or iritis was seen on long term acyclovir prophylaxis. However, a significant reduction in recurrence of stromal keratitis is noted with long term acyclovir

MEDICAL TREATMENT:

PRIMARY OCULAR AND PERIOCULAR HERPES SIMPLEX VIRUS INFECTIONS.

In the immunologically competent host, herpetic skin lesions remain fairly localized and are a self limited disease that resolves without scarring and often without specific therapy.

1. In the absence of corneal ulceration, prophylactic topical antiviral therapy with trifluridine or vidarabine or acyclovir to the eyes until the skin lesions resolve.
2. In the presence of corneal ulceration, simple debridement of the ulcer followed by antiviral ointment or drops for 14 to 21 days.
3. Eye shields in young children.
4. Topical povidone iodine to badly ulcerated skin,
5. Topical antibiotics if the cornea is ulcerated.
6. Cycloplegic if iritis is present.
7. Oral antiviral therapy with acyclovir, valacyclovir, or famciclovir for 1 week is used to limit corneal epithelial involvement and, although unproven, possibly reduce the risk of recurrences.

RECURRENT HERPES SIMPLEX VIRUS OCULAR DISEASE

HERPES SIMPLEX VIRUS BLEPHARITIS

1. Protect the globe.
2. Prophylactic antiviral ointment 3 times per day or drops 5 to 6 times per day until the lesion scabbed.

HERPES SIMPLEX VIRUS CONJUCTIVITIS

1. Topical trifluridine 9 times a day or Acyclovir 3% ointment 5 times a day for 2 weeks.

RECURRENT INFECTIOUS EPITHELIAL HERPES:

1. Gentle debridement of involved epithelium.
2. Acyclovir 3% ointment 5 times a day, or Trifluridine 1% 9times per day or Vidarabine 3% ointment 5 times per day for 14-21 days. Then the therapy is discontinued or rapidly tapered even if healing is not complete. It indicates viral resistance or trophic sterile ulceration.
3. Oral acyclovir 400 mg 3 times per day or famciclovir 500 mg 2 times per day or Valacyclovir 0.5 to 1 gm twice a day for 10 days.
4. Topical antibiotics BD while ulcers are present.

5. Cycloplegic if iritis present.
6. No place for the use of steroids in infectious epithelial disease uncomplicated by major stromal immune reaction.

TROPHIC POSTINFECTIOUS ULCERS:

Aimed at protecting the damaged basement membrane. There is no call for topical steroids or for antiviral therapy.

1. High water content therapeutic contact lens worn around the clock for 12 to 24 weeks.
2. Un preserved artificial tears four to five times a day while lens is worn and then for 4 to 6 months after removal of contact lens.
3. In some cases with major stromal edema use of mild steroids (0.125% prednisolone 1 to 4 times per day) with antiviral ointment as prophylaxis against recurrence.
4. Doxycycline or tetracycline to inhibit collagenase
5. Cycloplegic are necessary if iritis is present and also to increase soft contact lens tolerance.
6. Cyanoacrylate glue in ulcer bed to stop melting.
7. Patch graft or conjuctival flap, PKP if all else fails.

VIRAL NECROTIZING KERATITIS, INTERSTITAL KERATITIS, IMMUNE RINGS AND LIMBAL VASCULITIS:

Steroids still remain the prime therapeutic mode for stromal disease, with antiviral drugs used primarily as prophylaxis against recurrent infectious disease[37]. Therapeutically a general guideline is that if steroids have never been used in a particular eye, the physician should try not to use them.

1. In mild or off-visual axis cases artificial tears are sufficient.
2. Cycloplegic as needed for iridocyclitis.
3. Topical steroids are used if iridocyclitis progresses, visual axis is threatened or transplant surgery is anticipated or if steroids have been used previously. 0.1% dexamethasone or 1% prednisolone every 4 hours for severe disease to 0.125% prednisolone acetate every day to every other day for milder disease.
4. Topical antiviral and topical antibiotics as prophylaxis if steroids are used.

5. If the epithelium is ulcerated, reduce or stop topical steroids and start on systemic prednisolone (20-30mg orally twice daily for 7-10 days) and then taper.
6. Systemic acyclovir 400 mg BD for 1year or longer is shown to reduce the rate of recurrences.
7. If the eye remains uninflamed with little or no steroid treatment for six months, then keratoplasty can be done.

STROMAL DISCIFORM DISEASE:

It is highly steroid sensitive. Guidelines for treatment of disciform diseases are similar to those of antigen antibody complex-mediated disease. Artificial tears and dark glasses may also increase patient comfort until the reaction is resolved.

COMBINED EPITHELIAL AND STROMAL DISEASE

Active viral infection- start antiviral 1-2 days before steroid

If steroid already in use – then decreases dosage or stop topical steroids and start on systemic steroids and topical antiviral until epithelium start to heal.

If tropic ulcer with immune keratitis mild topical steroids and therapeutic contact lens

IRIDOCYCLITIS AND TRABECULITIS:

1. Cycloplegic
2. Topical steroids therapy may range from every 3 hours for severe involvement to once per day for mild disease, then gradually tapered and stop.
3. If the cornea has ulcerated or is melting systemic prednisolone 7 to 14 days and tapered.
4. Antiviral drops and topical antibiotics as prophylaxis
5. Carbonic anhydrase inhibitors, beta blockers, or both should be given if secondary glaucoma is present.
6. Oral acyclovir can be considered in severe cases.

INDICATIONS FOR SYSTEMIC ACYCLOVIR IN HERPETIC KERATITIS[28]:

Primary herpes simplex virus infection

Immuno compromised patient

Recurrent herpes simplex virus keratitis in children

As prophylaxis, post keratoplasty in patients with known history of herpes simplex keratitis

In severe cases of iridocyclitis / endothelitis

In stromal keratitis to prevent recurrence

SURGICAL MANAGEMENT

Surgical procedures may sometimes be necessary to treat acute and or chronic complications of herpes simplex keratitis .

PENETRATING KERATOPLASTY:

Penetrating keratoplasty is done not just to restore vision in a relatively quiet eye but in an eye with significant ulceration or perforation, or to remove the viral antigenic material lodged in the cornea and inciting repeated immune inflammatory episodes[8].

Factors leading to success rate greater than 80 percent

1. Operation on an eye uninflamed for 6 months.
2. No deep neovascularization or, if present, neovascularization involving less than one quadrant.
3. Intensive topical corticosteroid therapy may reduce vascularization prior to penetrating keratoplasty.
4. Use of fine (No.10-0 nylon) sutures.
5. Use of high doses of topical steroids in the immediate postoperative period and tapered use of steroids over the ensuing 3 or 4 months.

Controversy persists regarding the use of prophylactic antiviral therapy following penetrating keratoplasty. In reported clinical series of penetrating keratoplasty for herpetic keratitis the frequency of recurrent epithelial keratitis has ranged from 6% to 75% of cases[3], and the majority of these recurrences occurred within the first year following surgery. Antiviral therapy appeared to decrease the percentage of epithelial recurrences. Because allograft rejection accompanied epithelial recurrences in 25% of cases, antiviral therapy also appears to be associated with improved graft survival. Oral acyclovir may be preferable to chronic topical antiviral in patients with recent penetrating keratoplasty to prevent epithelial toxicity.

Other treatment modalities include use of cyanoacrylate glue in small perforations as a temporary measure. Conjuctival flap, tarsorraphy and botilinum induced ptosis may have a role in selected cases of nonhealing ulcers, particularly where donor tissue and expert postoperative management is not available.

IMMUNO COMPRAMISED PATIENTS

1) Topical antiviral ointment or drops in full therapeutic dosage

2) Systemic oral acyclovir 400mg 4 times/day for 2-3 wks or IV 5 mg/kg body wt for 3-5 days and then the patient is switched over to oral acyclovir 400 mg BD 5 times a day for 2-3 wks and then tapered to a long term maintenance therapy for 400mg orally twice daily to prevent recurrence.

3) Acyclovir resistant herpes simplex virus strains are increasingly isolated from HIV patients and do not produce thymidine kinase for drug activation. Alternative drug vidarabine which is activated by cellular and viral thymidine kinase and foscarnet which needs no phosphorylation can be used.

4) Topical α - 2A interferon treatment of herpes simplex virus resistant to multiple antiviral drugs has also been reported as effective

REFRACTIVE SURGERY

Herpes simplex virus recurrences are reported from day one after LASIK. This is due to reactivation of latent virus. Many prefer not to do refractive surgery in patients with a history of herpes. A good history prior to refractive surgery is a must. Eye should be quiet for at least 2 yrs with no herpes simplex virus infection. Prophylactic acyclovir 400 mg oraly BD 3times/day starting 1-2 wks prior & continue for several weeks to months after refractive surgery.

REVIEW OF LITERATURE

1. Jagjit S. Saini; Ritu Agarwal MS. A study of clinical pattern of recurrent herpes simplex keratitis. IJO Vol47;1999;11-14,

67.75% of the patient belong to the age group of 31-60 yrs. Men were found to have the disease 4 times more often than women. Clinical pattern of recurrence was of the same type following first episode of stromal keratitis and epithelial keratitis in 84% and 72.7% of the eyes respectively. Almost 3 times longer disease free interval was found between epithelial and stromal keratitis.

2. Wilhelmus KR , Dawson CR, Barron BA, Bacchetti P, Gee L, Jones DB. A study of risk factors for herpes simplex virus epithelial keratitis recurring during treatment of stromal keratitis or iridocyclitis (for Herpetic eye disease study group) BJO 1996;80:969-72

Dendritic and geographic epithelial keratitis occurred only in 4.6% of the patients with stromal keratitis.

3. Predictors of recurrent herpes simplex virus keratitis by herpetic eye disease study group; Cornea 2001 march; 20(2)123-8.

Age, gender, ethnicity and non-ocular herpes were not significantly associated with recurrences and no seasonal effects were observed. No factor other than the number of previous episodes of stromal keratitis appeared predictive of its development. Patients with at least one previous episode of stromal keratitis were 10 times more likely to have a subsequent episode of stromal keratitis. Risk of developing epithelial keratitis is only weakly related to the number of previous episodes.

4. Liesegang TJ: A study of epidemiology of ocular herpes simplex. Natural history in Rochester, Minn, 1950 through 1982; Arch ophthalmol 1989 Aug; 107(8):1160-5

Ocular herpes simplex affecting both eyes at the same and/or different episodes was seen in 11.9% of the patients.

5. Uchio.E, Hantano H, Mitsui K, Sugita M, Okada K, Goto K , Kagiya M, Enomoto Y, Ohno S. A retrospective study of Herpes simplex keratitis over last 30 yrs; Jpn J ophthalmol;1994;38(2) 196-201.

The age of the patient ranged from 1-72 yrs mean (38.4yrs). Bilateral herpetic disease was seen in 10.4 % of patients. Epithelial keratitis and stromal keratitis was found in 57. 3% and 39.3% respectively.

6. Wilhelmus KR, Coster DJ, Donovan HC, Jones BR, Falcon MG. A study of prognostic indicators of herpetic keratitis. Analysis of 5 year observation period after corneal ulceration; Arch. Ophthalmol 1981; 99 ;1578-82.

63% of epithelial keratitis tends to recur more often as epithelial disease.

7. Zhonghu Yan Ke Za Zhi. A clinical analysis of recurrences of herpes simplex keratitis; 1989 Nov 25(6); 326-8. The recurrence rate was significantly higher in cases with stromal involvement or iritis and slightly higher in children or older patients.

8. Wishart MS, Darougar S, Viswalingam ND. A study of recurrent herpes simplex virus ocular infection; epidemiology and clinical features; Br J ophthalmol. 1987:71(9) 669-72.

There was no significant difference between recurrence rates in males and females. 49% had less than 2 recurrent attacks. 40% had 3-5 attacks and 11% had between 6 and 15 attacks.

9. Shuster JJ, Kaufman HE, Nesburn AB. A statistical analysis of rate of recurrence of herpes virus ocular disease; Am J ophthalmol 1981;91: 328-31

The time difference in disease free interval between epithelial and stromal keratitis is statistically significant p (<0.005)

10. "A study of virology and clinical features of Herpes simplex keratitis in South India" Internet journal of ophthalmology 2: 18-26; 1977.

Has showed 43.33% of dendritic ulcer 11.33% of geographic ulcer 11.33% of SPK, 16.66% of Disciform keratitis and 6.66% immune ring. 51.51% with spontaneous onset, 24.24% had fever while 6.06% had ocular trauma and 13.63% had exposures to sunlight and 4.54% had URI.

AIM OF THE STUDY

The main objective of the study is

To study the clinical pattern

To assess the disease free intervals

To assess the visual outcome

Of recurrent herpes simplex keratitis in Government Rajaji Hospital – Madurai.

MATERIALS AND METHODS

46 patients were examined over a period of 1 year at the cornea services Government Rajaji Hospital – Madurai

All patients with a clinically documented recurrent herpes simplex infection who were treated in our hospital were included in the study.

They were analysed retrospectively using a standardized questionnaire which assessed the age, sex, clinical type of previous herpes simplex virus corneal disease, duration of disease free interval, trigger factors if any, laterality of the disease.

A detailed slit lamp examination was done and the clinical type of herpes simplex keratitis was assessed.

A diagnosis of epithelial keratitis was made when a branching linear dendritic ulcer or a geographic ulcer appearing as a broad area of epithelial defect with amoeboid borders was seen.

Stromal keratitis was diagnosed when deeper layers of corneal stroma showed diffuse infiltration and odema of the stroma with or without necrosis, ulceration and vascularization. Necrotizing keratitis, interstitial keratitis, immune ring, limbal vasculitis, disciform keratitis are included in this.

Keratouveitis was diagnosed when there was a severe corneal odema with or without vascularization and marked signs of anterior uveitis. Since it was difficult to differentiate clinically mild keratouveitis and endothelitis, both were clubbed together for the pattern of analysis of recurrences.

Neurotropic ulcer was diagnosed when the patients presented with persistent epithelial defect with grey thickened elevated borders.

The uniform treatment policy was adopted. Epithelial keratitis was treated with topical 3%acyclovir ointment 5 times a day for 2-3 weeks and topical ciprofloxin eye drops BD.

Stromal keratitis was treated with topical prednisolone acetate in dosage according to the disease severity along with prophylactic 3% Acyclovir ointment BD and prophylactic ciprofloxin drops BD along with homatropine eye drops BD.

Iridocyclitis was treated in the same way as stromal keratitis. Secondary glaucoma was treated with 0.5% timolol eye drops BD.

When the patient has a combined pattern of epithelial & Stromal keratitis he was initially treated with topical 3% acyclovir ointment, homatropine eye drops BD and ciprofloxin eye drops BD until the epithelium starts healing and then was started on prenisolole acetate drops.

These patients were followed up for one year using slit lamp examinations at 3 specified follow up visits during the one year and at additional times when the patient developed new ocular complaints.

Of the 46 patients 12 patients lost follow up and were excluded from the study.

The pattern of recurrence was studied for epithelial and stromal keratitis.

The average disease free interval was calculated for epithelial and stromal keratitis taking into account only those eyes which recurred purely in the same pattern as its initial presentation.

RESULTS AND OBSERVATION

AGE DISTRIBUTION

Table - 1

Age	No.of patients	Percentage
0-10	0	0
11-20	3	8.82
21-30	3	8.82
31-40	10	29.41
41-50	11	32.36
51-60	3	8.82
61-70	4	11.77
>71	0	0
Total	34	

Of the total of 34 patients the average age was found to be 40.38 yrs with the range between (12 – 69). 21 patients (61.77%) of the patients were in the age group of 31 – 50 yrs.

SEX DISTRIBUTION

Table -2

Gender	No. of patients	Percentage
Male	18	52.94
Female	16	47.06

Men and women were found to have almost equal incidence of the disease with men accounting for 52.94% (18 patients) and women 47.06% (16 patients).

LATERALITY OF THE DISEASE

Table - 3

Laterality	No. of patients	Percentage
Unilateral	31	91.17
Bilateral	3	8.83

Bilateral disease was seen in 3 patients accounting for 8.83 % of the patients. Of the 3 patients one patient showed simultaneous involvement. Clinical manifestations were similar in all those with bilateral disease pattern.

PATTERN OF INITIAL PRESENTATION

Table - 4

Pattern of initial Presentation	No. of Eyes	Percentage
Epithelial	20	54.05
Stromal	11	29.72
Epithelial + Stromal	3	8.10
Uveitis	3	8.10

Epithelial keratitis was found in 54.05% (20 eyes) of the 34 eyes and stromal keratitis was found in 29.72% (11 eyes). 8.10% of eyes (3 eyes) showed a combined pattern of epithelial and stromal keratitis and 8.10% (3 eyes) showed features of uveitis.

PATTERN OF INITIAL PRESENTATION

Table - 5

Pattern	No. of Eyes	Percentage
Epithelial (N = 20)		
Dendritic	12	38.24
Geographic	4	11.76
SPK	4	11.76
Stromal (N = 11)		
Disciform	7	18.91
Interstitial keratitis	4	10.81
Epithelial + Stromal	3	8.82
Uveitis	3	8.82

It was found that of the 20 cases with epithelial keratitis 12 (38.24%) were found have a dendritic pattern 4 (11.76%) with Geographic pattern and 4 (11.76%) had Superficial punctate keratitis. Of the 11 patients with stromal keratitis 7 (18.91%) were found have disciform pattern while 4 (11.76%) had Interstitial keratitis.

PATTERN OF RECURRENCE IN EPITHELIAL KERATITIS

Table - 6

Pattern of recurrence Epithelial	No. of Eyes	Percentage
Epithelial	13	65%
Stromal	6	30%
Metaherpetic	1	5%

Of those with epithelial disease (20 eyes) the pattern of recurrence was in the form of epithelial disease every time in 13 eyes (65%) and 6 eyes (30%) demonstrated stromal disease. One patient (5%) showed a metaherpetic pattern on recurrence.

PATTERN OF RECURRENCE IN STROMAL KERATITIS

Table - 7

Pattern of recurrence	No. of Eyes	Percentage
Epithelial	1	9%
Stromal	9	82%
Epithelial + Stromal	1	9%

Of the 11 eyes which presented initially with stromal keratitis it was found that 9 eyes recurred only as stromal keratitis which accounting for 81.81% of eyes. One (9%) eye recurred as epithelial keratitis while one (9%) more eye had a combined pattern of epithelial and stromal keratitis.

PATTERN OF RECURRENCE FOLLOWING INITIAL UVEITIS

Table - 8

Pattern of recurrence	No. of Eyes	Percentage
Epithelial	1	33.33%
Stromal	0	0%
Uveitis	2	66.66%

Of the 3 patients with Uveitis 2 (66.66%) to of them recurred in the same pattern while 1 patient (33.33%) recurred as epithelial keratitis.

PATTERN OF RECURRENCE FOLLOWING INITIAL EPITHELIAL + STROMAL KERATITIS

Table - 9

Pattern of recurrence	No. of Eyes	Percentage
Epithelial	Nil	-
Stromal	1	33.33%
Epithelial + Stromal	2	66.66%

Of the 3 patients with epithelial and stromal keratitis 2 (66.6%) of them recurred in the same pattern while 1 patient (33.3%) recurred with stromal keratitis only.

NUMBER OF RECURRENCES

Table - 10

Number of recurrence	No. of Eyes	Percentage
1 or 2	23	62.16
>2	14	37.83

Eyes recruited in this study demonstrated 1-4 recurrences. 23 eyes (62.16%) showed only 1 or 2 recurrences while 14 eyes (37.83%) showed more than 2 recurrences.

PATTERN OF RECURRENCE AND NUMBER OF RECURRENCE

Table - 11

Pattern	Total	No of eyes with > 2 recurrence	Percentage
Epithelial	20	3	15
Stromal	11	5	45.45
Epithelial+ Stromal	3	3	100
Uveitis	3	3	100

Also only 3 of the 20 eyes (15%) with epithelial keratitis showed more than 2 recurrences while 5 of the 11 eyes (45.45%) with stromal keratitis showed more than 2 recurrence and all the 3 cases with epithelial and stromal keratitis showed more than 2 recurrences and all three cases with Uveitis showed more than 2 recurrences.

DISEASE FREE INTERVAL

Table -12

Pattern of recurrence	Disease free interval (months)
Epithelial	21.52
Stromal	7.09
Epithelial+ Stromal	6.75
Uveitis	8.55

Patients with recurring stromal keratitis were found to have an average disease free period of 7.09 months between attacks. Those with epithelial + stromal keratitis were also found to have a shorter time interval of about 6.75 months between the attacks and those with Uveitis were found have an average disease free period of 8.55 months. Epithelial recurrences were found to have a longer disease free interval of an average of 25.52 months in between episodes.

DISEASE FREE INTERVAL IN BETWEEN RECURRENCE

Table - 13

	Disease free interval (months)			
	I	**II**	**III**	**IV**
Epithelial	22	19	10	-
Stromal	8.86	6.16	5.75	4.5
Epithelial+ Stromal	10.5	8.5	4.5	3.5
Uveitis	14	10	4.5	3

It was found that the disease free interval in between subsequent attacks decreased in all cases. In case of epithelial keratitis the average disease free interval in first recurrence was found to be 22 months and second recurrence 19months and third recurrence 10months. In stromal keratitis the average disease free interval for 1^{st} , 2^{nd} , 3^{rd} and 4^{th} recurrences was found to be 8.86 months , 6.16months, 5.75months and 4.75 months respectively while for cases with epithelial + stromal keratitis it was 10.5 months, 8.5months, 4.5months and 3.5months respectively and in Uveitis it was 14 months, 10months, 4.5 months and 3 months respectively .

VISUAL OUTCOME FOLLOWING TREATRMENT.

Table - 14

No.of recurrence	Total	Patients who lost 2 or more lines of vision	
		No.	Percentage
1 or 2	23	2	8.69%
>2	14	9	64.28%

Table - 15

Patterns of recurrence	Total	Patients who lost 2 or more lines of vision	
		No.	Percentage
Epithelial	20	3	15%
Stromal	11	4	36.36%
Epithelial + Stromal	3	2	66.6%
Uveitis	3	2	66.6%

It is being observed from the study that while only 2 of the 23 patients with less than 2 recurrence showed a decrease in vision by 2 lines 9 of the 14 patients with >2 recurrence (64.28%) showed a decrease in vision by 2 or more lines

Also it was seen that while only 15% of patients with epithelial keratitis showed a decrease in vision by 2 lines or more 36.36% of patients with stromal keratitis and 66.66% of patients with epithelial + stromal Keratitis and uveitis showed a loss of vision by 2lines or more.

TRIGGER FACTORS

Table - 16

Trigger factor	No. of Eyes	Percentage
Fever	5	14.7%
Ocular trauma	3	8.83%
Psychological Stress	1	2.94%
URI	3	8.83
Spontaneous	22	64.70%

A trigger for recurrence was identified only in 10 patients (29.42%). The major precipitating factors for recurrences were a history of Fever in 5 patients (14.17%); ocular trauma in 3 patients (8.84%); psychological stress in 1 patient (5.88%) and Upper respiratory tract infection in 3 patients (8.83%). Majority – 21 of the patients (70.58%) showed only a spontaneous onset of recurrence.

COMPLICATIONS

Table - 17

Complication	No. of Patients
Metaherpetic ulcer	1
Glaucoma	1
Corneal scarring	3

During the study it was observed that 1 patient with epithelial keratitis while on treatment developed a metaherpetic pattern. One patient with Uveitis developed secondary glaucoma. 3 patients with stromal keratitis developed residual stromal scarring, while almost all cases of epithelial keratitis healed without much residual effect.

DISCUSSION

The average age was found to be 40.38 yrs with the range between (12 – 69). 21 patients (61.77%) fall in the age group of 31 – 50 yrs. This is comparable with the study of Saini and Agarwal et al which shows 67.5% of patients in the age group of 31 – 60 yrs and also with Wilhelmus KR, Coster DJ, Donovan HC, Jones BR, Falcon MG et al which shows a higher incidence of herpetic keratitis at 40 – 60 yrs.

Men and women were found to have almost equal incidence of the disease with men accounting for 52.94% (18 patients) and women 47.06% (16 patients).

3 patients showed bilateral involvement accounting for 8.83 % of the patients and only one of them showed simultaneous involvement. Clinical manifestations were similar in both eyes. This agrees with the findings of Uchio. E, Hantano H, Mitsui K, Sugita M, Okada K, Goto K , Kagiya M , Enomoto Y, Ohno S et al and Liesegang TJ et al who reported 10.4% and 11.9% of bilateral disease respectively.

In their initial presentation 54.05% (20 eyes) of the eyes showed epithelial pattern and stromal keratitis was found in 29.72% (11 eyes). 8.10% of eyes (3 eyes) had a combined pattern of epithelial and stromal keratitis and 8.10% (3 eyes) showed features uveitis. This is consistent with of Uchio.E, Hantano H, Mitsui K, Sugita M, Okada K, Goto K , Kagiya M , Enomoto Y, Ohno S et al who in their study found 57.3% of epithelial keratitis and 39.3% of stromal keratitis but in contrast with Saini and Agarwal et al who showed 62.5% of stromal keratitis and 27.5% of epithelial keratitis.

Among the 20 cases with epithelial keratitis 12 (38.24%) were found have a dendritic pattern, 4 (11.76%) with Geographic pattern and 4 (11.76%) had Superficial punctate keratitis. Of the 11 patients with stromal keratitis 7 (18.91%) were found have disciform pattern while 4 (11.76%) had interstitial keratitis. On reviewing the literature "A study of Virology & clinical features of herpes simplex keratitis in south India" has showed 43.33% of dendritic ulcer 11.33% of geographic ulcer 11.33% of SPK, 16.66% of Disciform keratitis and 6.66% immune ring.

Of those with epithelial disease (20 eyes) the pattern of recurrence was in the form of epithelial disease every time in 13 eyes (65%) and 6 eyes (30%) demonstrated stromal disease. One patient (5%) showed a metaherpetic pattern on recurrence. This is in agreement with Saini and Agarwal et al and with Wilhelmus KR, Coster DJ, Donovan HC, Jones BR, Falcon MG et al who state that previous dendritic and geographic ulcers lead to subsequent dendrites and geographic ulcers.

Similarly among the 11 eyes which presented initially with stromal keratitis it was found that when 9(81.81%) of eyes recurred only as stromal keratitis only one (9%) eye recurred as epithelial keratitis while another one (9%) eye had a combined pattern of epithelial and stromal keratitis. This goes in hand with the study of Saini and Agarwal et al which showed 84% of stromal keratitis recurring only as stromal keratitis. Wilhelmus KR, Dawson CR, Barron BA, Bacchetti P, Gee L, Jones DB et al (for Herpetic eye disease study group) also shows low recurrences of epithelial disease in eyes manifesting herpes simplex virus stromal disease.

Of the 3 patients with Uveitis, 2 (66.66%) of them recurred in the same pattern while 1 patient (33.33%) recurred as epithelial keratitis.

Of the 3 patients with epithelial and stromal keratitis, 2 (66.6%) of them recurred in the same pattern while 1 patient (33.3%) recurred with stromal keratitis only. Thus it is seen that Herpes simplex keratitis often recurs in the same clinical pattern as the first episode, which could be due to the concept that viral strains determine the clinical pattern of the disease.

Eyes recruited in this study demonstrated 1-4 recurrences. 23 eyes (62.16%) showed only 1 or 2 recurrences while 14 eyes (37.83%) showed more than 2 recurrences. This is almost consistent with Wishart MS, Darougar S, Viswalingam ND et al studies which showed 40% of patients showing 3-5 attacks and with Saini and Agarwal et al showing 27.5% of patients showing more than 2 recurrences.

It was also observed when only 15% of the eyes with epithelial keratitis showed more than 2 recurrences 45.45% with stromal keratitis

showed more than 2 recurrence and all the 3 cases with epithelial and stromal keratitis showed more than 2 recurrences and all three cases with Uveitis showed more than 2 recurrences. This is in agreement with Zhonghu Yan Ke Za Zhi et al who state that the recurrence rate was significantly higher in cases with stromal involvement or iritis. This could be because more virulent strains are involved in stromal keratitis and that this therapeutic regimen had little effect on viral particle related stromal keratitis.

It was also observed that while patients with recurring stromal keratitis have an average disease free period of 7.09 months between attacks and those with epithelial + stromal keratitis had 6.75 months between the attacks and those with Uveitis were found have an average disease free period of 8.55 months. But epithelial recurrences were found to have a longer disease free interval of an average of 25.52 months in between episodes. This is consistent with the finding of Saini and Agarwal et al who found almost a 4 times longer average disease free interval in epithelial keratitis when compared to stromal keratitis .This also goes in hand with Shuster JJ, Kaufman HE, Nesburn AB, et al

who stated that the time difference in disease free interval between epithelial and stromal keratitis is statistically significant ($p<0.005$).

It was found that the disease free interval in between subsequent attacks decreased in all cases.

A trigger for recurrence was identified only in 10 patients (29.42%). The major precipitating factors for recurrences were a history of fever in 5 patients (14.17%); ocular trauma in 3 patients (8.84%); psychological stress in 1 patient (5.88%) and Upper respiratory tract infection in 3 patients (8.83%). This suggests that some form of physical or emotional stress acts as a trigger. Majority – 21 of the patients (70.58%) showed only a spontaneous onset of recurrence. On reviewing the literature "A study of virology and clinical features of Herpes simplex keratitis in South India" showed 51.51% with spontaneous onset, 24.24% had fever while 6.06% had ocular trauma and 13.63% had exposures to sunlight and 4.54% had URI.

During the study 1 patient with epithelial keratitis while on treatment developed a metaherpetic pattern. Metaherpetic ulcer was treated with intermittent 48 hr pressure patching with ciprofloxin eye ointment artificial tears qid and continued for 2-3 months after removal of patch. Homatropine eye drops BD was added. One patient with Uveitis developed secondary glaucoma and was treated with 0.5%timolol eye dps BD. 3 patients with stromal keratitis developed residual stromal scarring, while almost all cases of epithelial keratitis healed without much residual effect. 2 of the patients with corneal scaring had deep vascularisation and PKP was deferred and another patient is kept on follow up to take up for PKP after his eyes remain quiet for 6 months.

Only 2 of the 23 patients with less than 2 recurrence showed a decrease in vision by 2 lines, 9 of the 14 patients with >2 recurrence (64.28%) showed a decrease in vision by 2 or more lines. This is because with each recurrence there is increased risk of stromal inflammation and consequent permanent corneal scarring leading to decrease in visual outcome.

Also it was seen that while only 15% of patients with epithelial keratitis showed a decrease in vision by 2 lines or more, 36.36% of patients with stromal keratitis and 66.66% of patients with epithelial + stromal Keratitis and uveitis showed a loss of vision by 2lines or more. This could again be because of the increased inflammation and scarring associated with these patterns of disease.

CONCLUSION

Herpes simplex eye infection is an important cause of corneal blindness. Recurrences of the disease are the major cause of ocular morbidity.

It is being seen from the study that herpes simplex disease often recurs in the same clinical pattern as the first episode. It is also seen that stromal involvement though accounting for only about 30% of the initial presentation, it is the one which shows more number of recurrence at a shorter interval of time than that of epithelial involvement. Thus stromal keratitis accounts for the major cause of ocular morbidity due to herpes simplex keratitis. Hence an early recognition and prompt treatment is necessary and more light is to be shown on the ways of preventing recurrences through subsequent studies.

CLINICAL PATTERN OF RECURRENCE HERPES SIMPLEX KERATITIS

PROFORMA

1) Name :
2) Ip/Op No :
3) Age :
4) Sex :
5) Detail of previous attack

Initial attack

Date :

Pattern :

Treatment :

Trigger factor :

Disease free interval:

Recurrences

1		2	
Date	:	Date	:
Pattern	:	Pattern	:
Treatment	:	Treatment	:
Trigger factor	:	Trigger factor	:
Disease free interval	:	Disease free interval	:
3		4	
Date	:	Date	:
Pattern	:	Pattern	:
Treatment	:	Treatment	:

Trigger factor :

Disease free interval :

Trigger factor :

Disease free interval:

6) Details of follow up

1) Date

S/L Examination -Lids

Conjuctiva

Cornea

AC

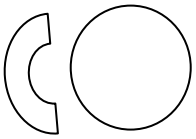
Iris

Pupil

Lens

Staining

Vision



2) Date

S/L Examination - Lids

Conjuctiva

Cornea

AC

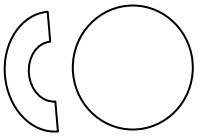
Iris

Pupil

Lens

Staining

Vision



3) Date

S/L Examination – Lids

Conjuctiva

Cornea

AC

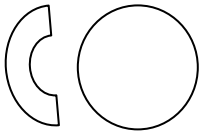
Iris

Pupil

Lens

Staining

Vision



7) Number of recurrence

8) Laterality of the Disease

Unilateral

Bilateral

9) Trigger Factors

Fever

Trauma

Ocular Surgeries

Non ocular surgeries

Upper Respiratory tract infection

Exposure to UV rays (sunlight)

Menstruation

Psychological stress

Steroid Exposure

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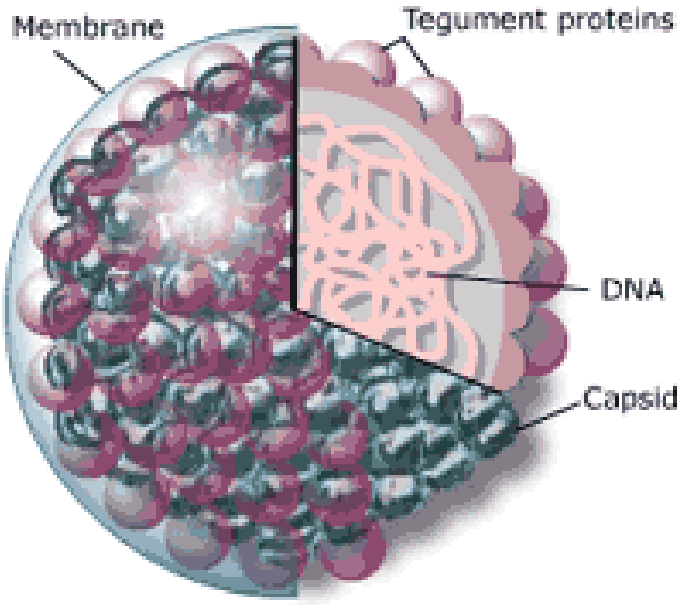
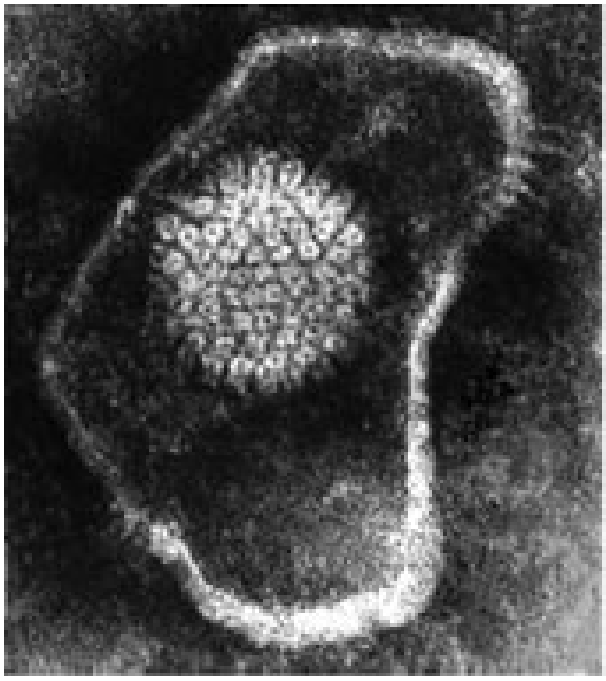
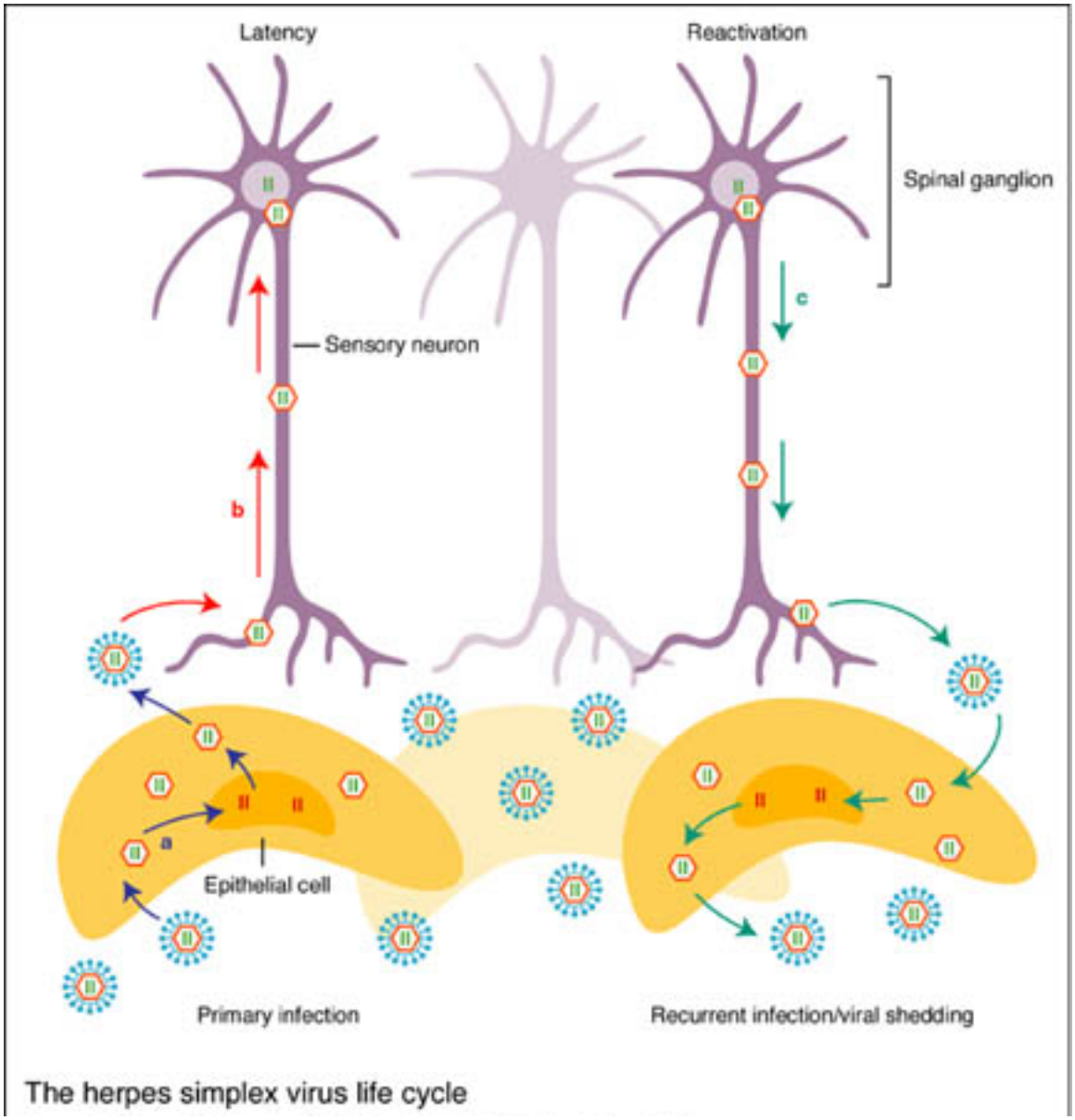


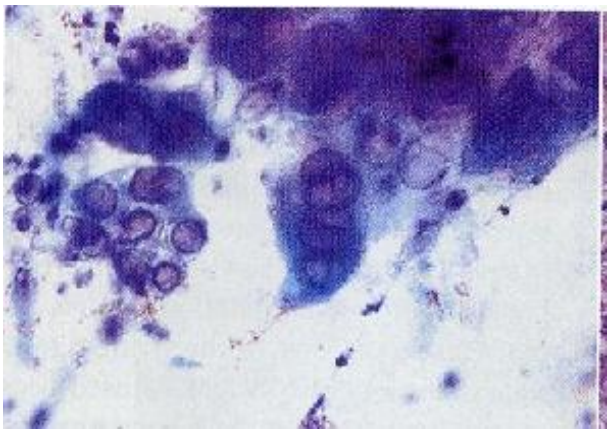
HERPES SIMPLEX VIRUS



ELECTRON MICROSCOPIC PICTURE OF HEPES SIMPLEX VIRUS

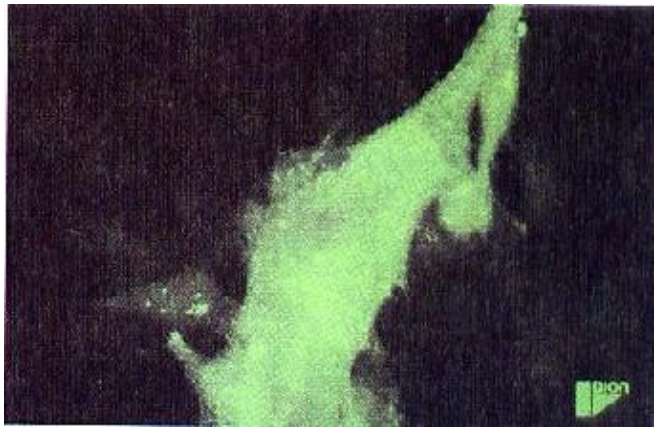


The herpes simplex virus life cycle



TZANCK SMEAR WITH LIPSCHUT BODIES

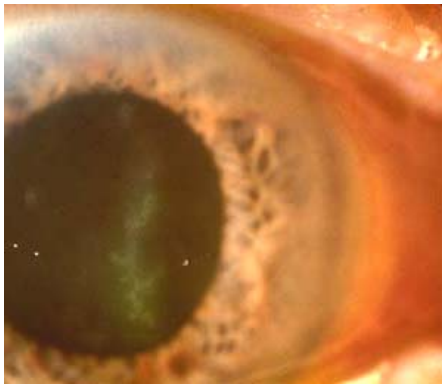
TISSUE CULTURE



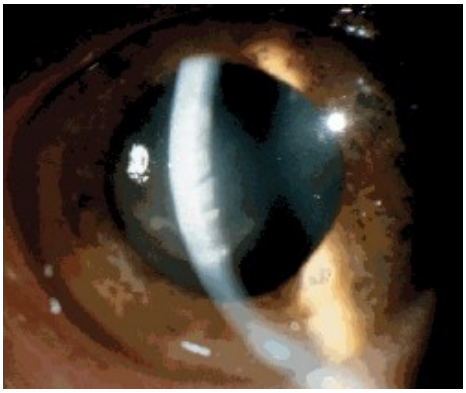
FLORESCENT ANTIBODY STAINING

-

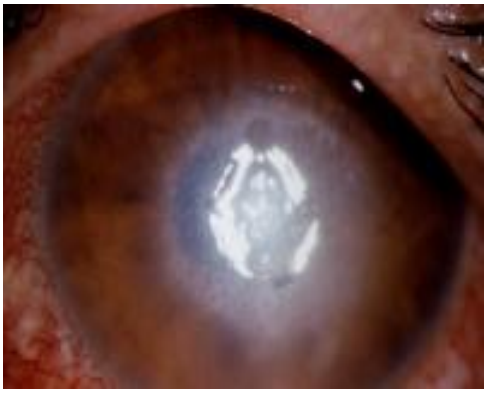
DENDRITIC ULCER

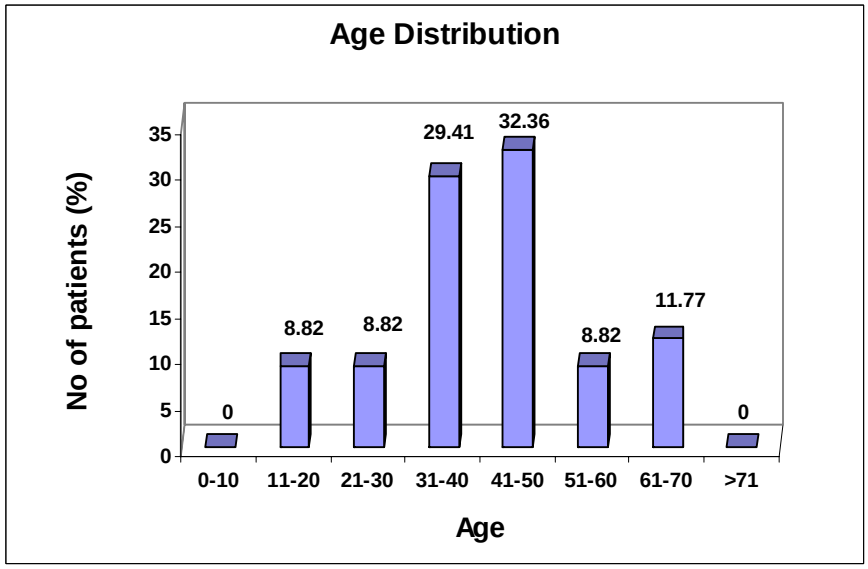


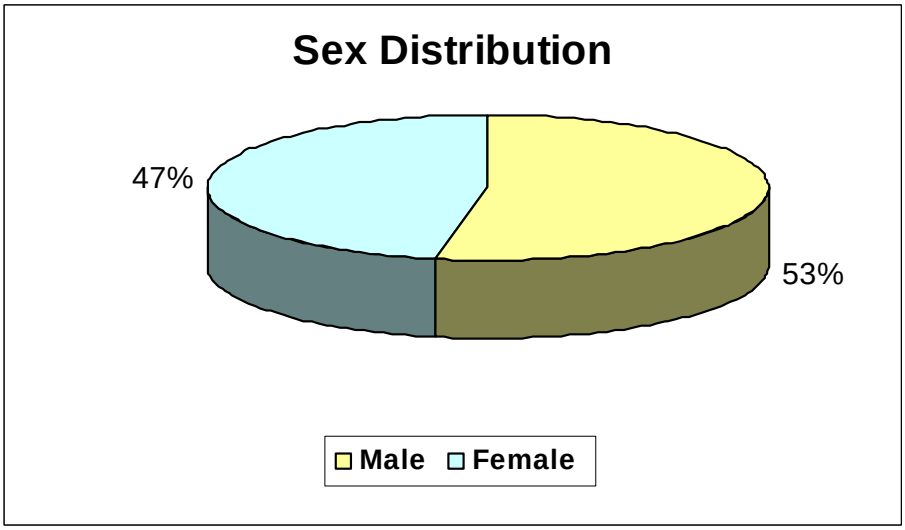
DISCIFORM KERATITIS

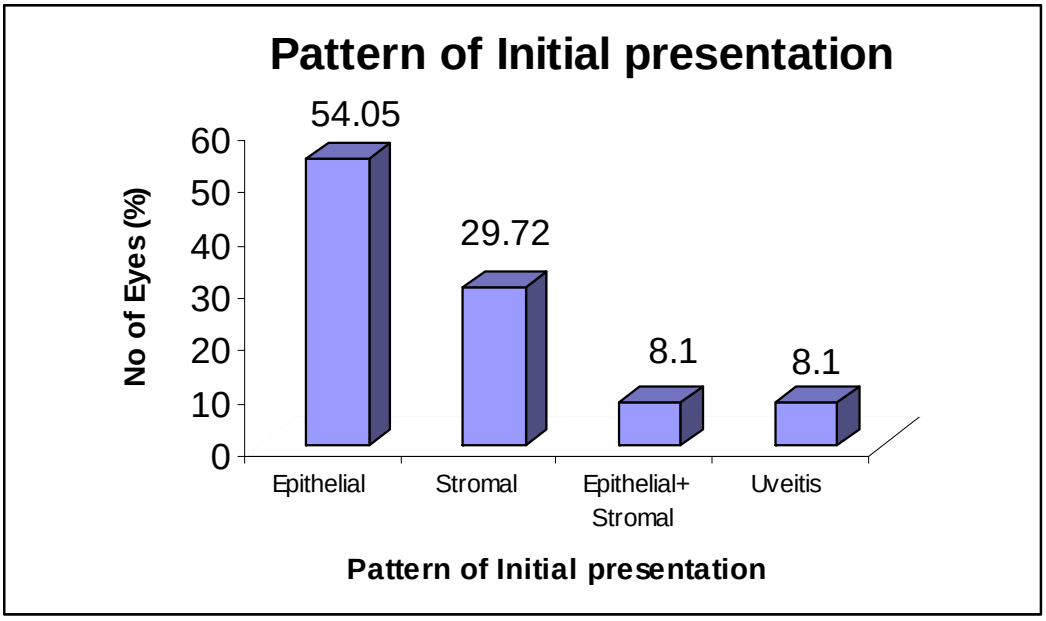


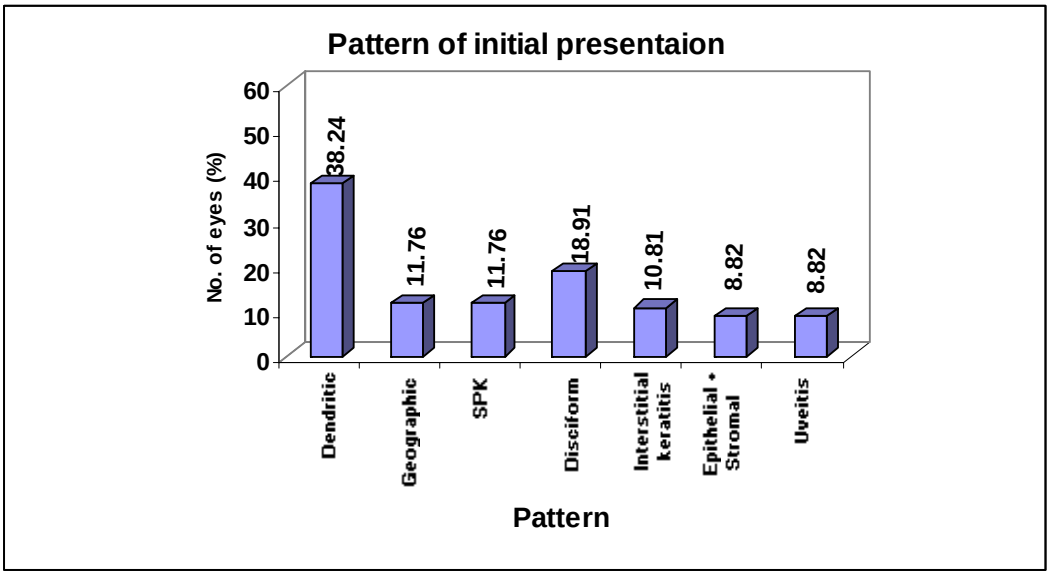
COMBINED EPITHELIAL AND STROMAL KERATITIS

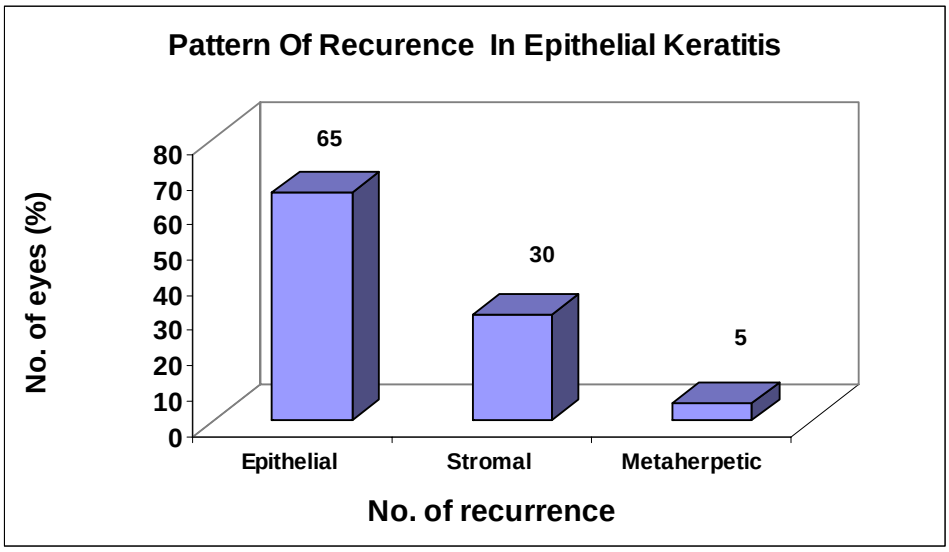


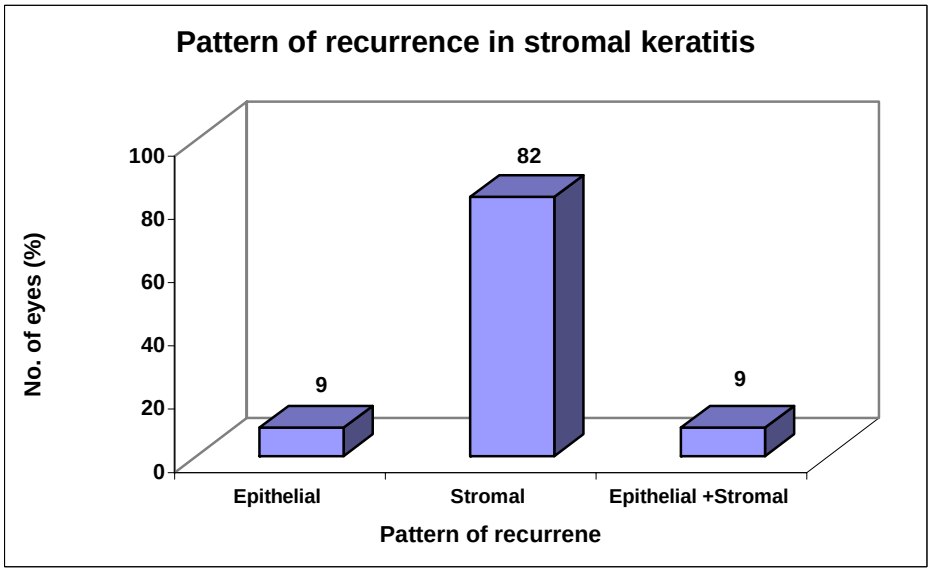

Age Distribution
No of patients (%)
35
30
25
20
15
10
5
0
0
8.82
8.82
29.41
32.36
8.82
11.77
0
0-10
11-20
21-30
31-40
41-50
51-60
61-70
>71
Age

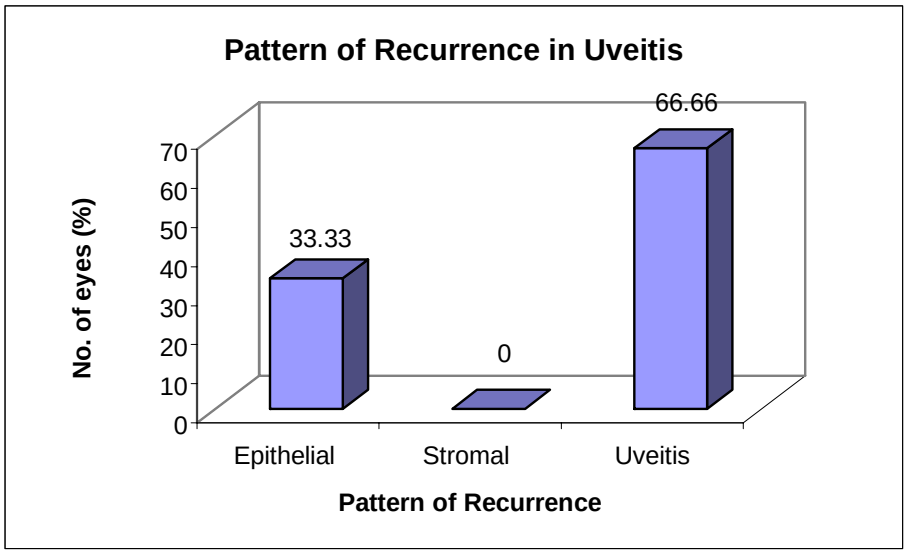

Sex Distribution
47%
53%
Male
Female

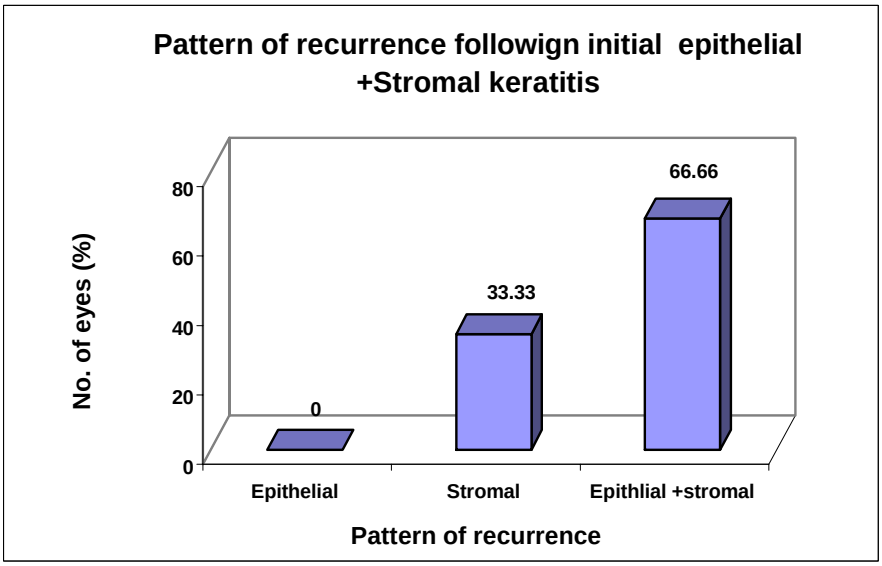

Pattern of Initial presentation
54.05
29.72
8.1
8.1
60
50
40
30
20
10
0
No of Eyes (%)
Epithelial
Stromal
Epithelial+ Stromal
Uveitis
Pattern of Initial presentation

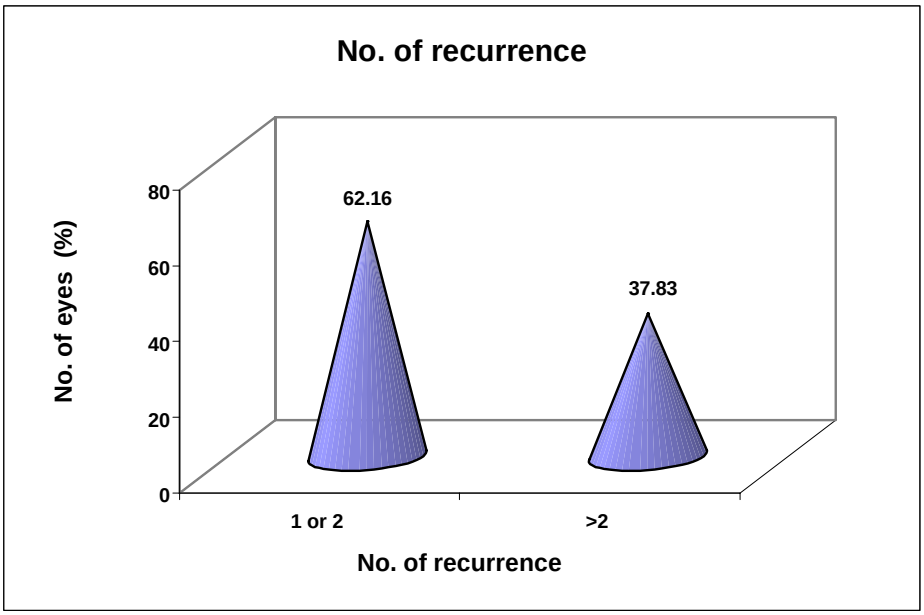

Pattern of initial presentaion
60
50
40
30
20
10
0
No. of eyes (%)
38.24
11.76
11.76
18.91
10.81
8.82
8.82
Dendritic
Geographic
SPK
Disciform
Interstitial keratitis
Epithelial + Stromal
Uveitis
Pattern

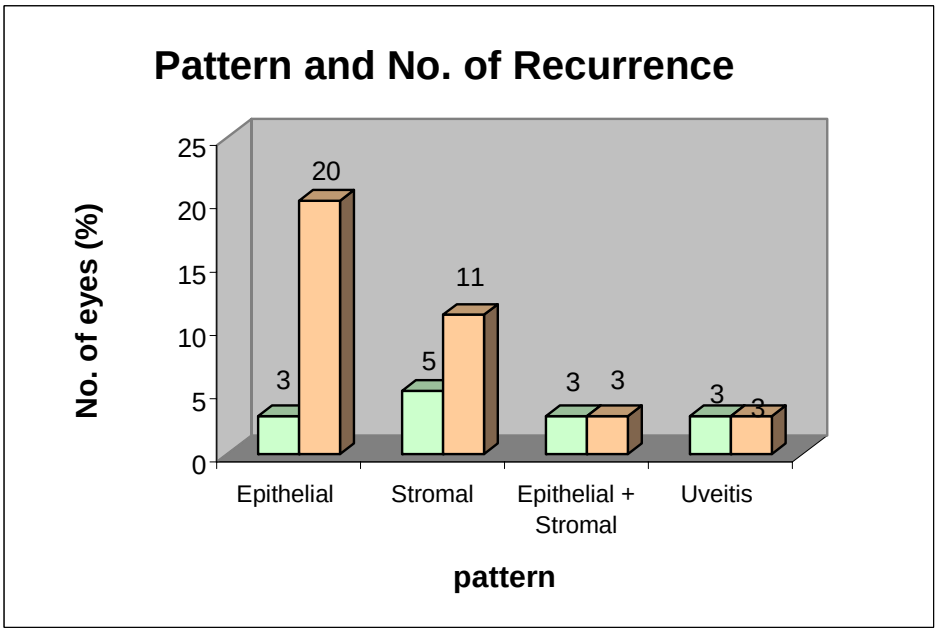

Pattern Of Recurence In Epithelial Keratitis
No. of eyes (%)
80
70
60
50
40
30
20
10
0
65
30
5
Epithelial
Stromal
Metaherpetic
No. of recurrence

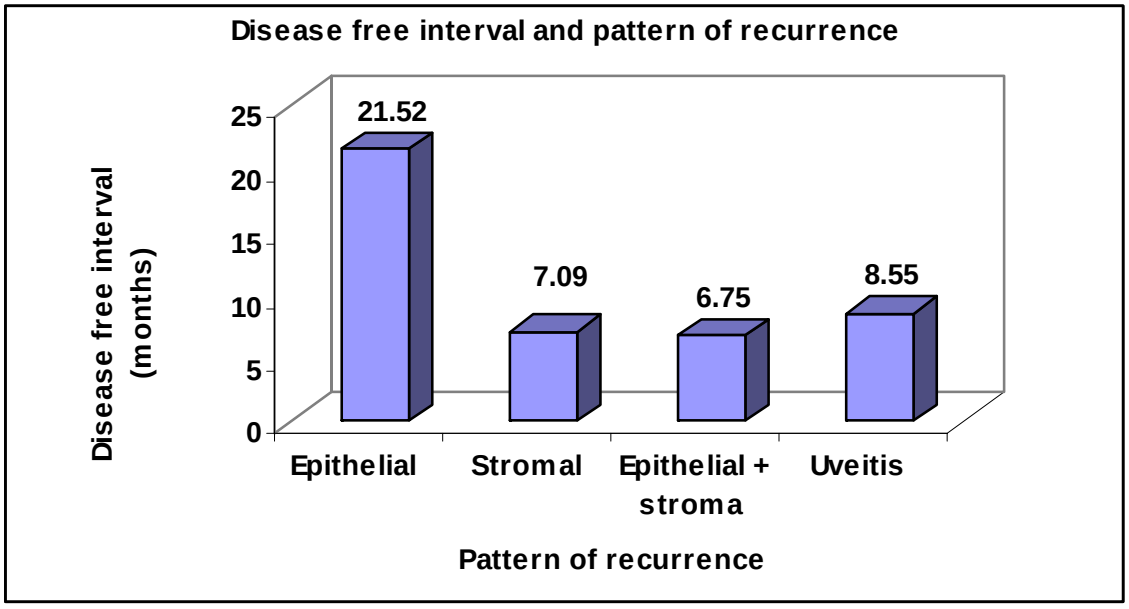

Pattern of recurrence in stromal keratitis
No. of eyes (%)
100
80
60
40
20
0
9
82
9
Epithelial
Stromal
Epithelial +Stromal
Pattern of recurrene

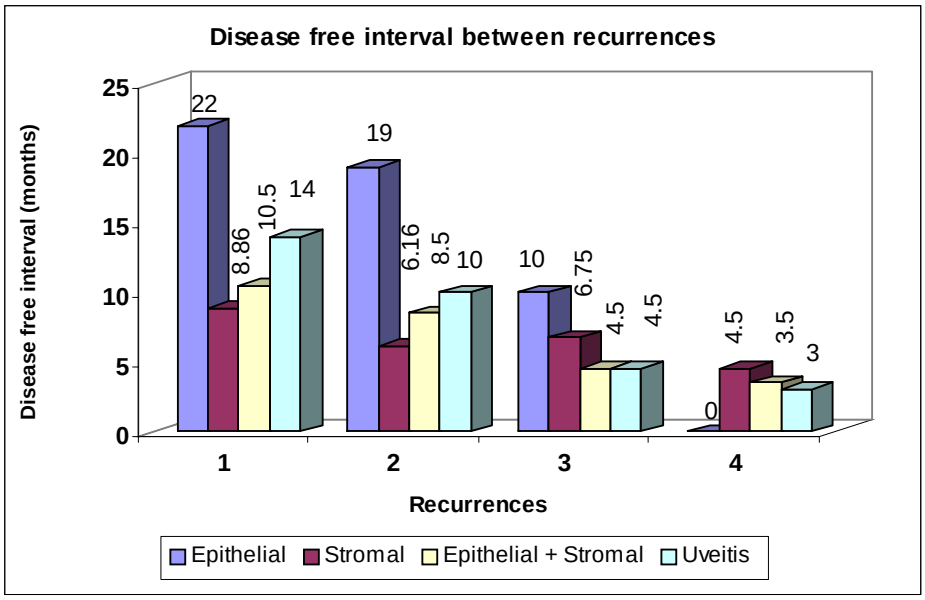

Pattern of Recurrence in Uveitis
No. of eyes (%)
70
60
50
40
30
20
10
0
33.33
0
66.66
Epithelial
Stromal
Uveitis
Pattern of Recurrence

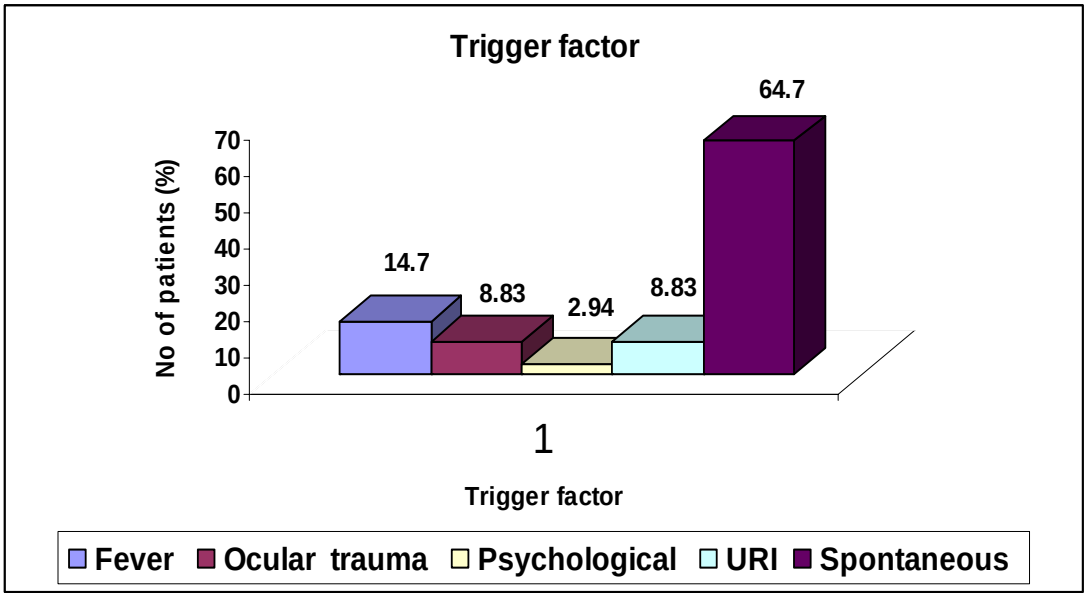

Pattern of recurrence followign initial epithelial +Stromal keratitis
No. of eyes (%)
80
60
40
20
0
0
33.33
66.66
Epithelial
Stromal
Epithlial +stromal
Pattern of recurrence


No. of recurrence
No. of eyes (%)
80
60
40
20
0
62.16
37.83
1 or 2
>2
No. of recurrence


Pattern and No. of Recurrence
No. of eyes (%)
25
20
15
10
5
0
3
20
5
11
3
3
3
3
Epithelial
Stromal
Epithelial + Stromal
Uveitis
pattern


Disease free interval and pattern of recurrence
Disease free interval (months)
25
20
15
10
5
0
21.52
7.09
6.75
8.55
Epithelial
Stromal
Epithelial + stroma
Uveitis
Pattern of recurrence


Disease free interval between recurrences
Disease free interval (months)
25
20
15
10
5
0
22
8.86
10.5
14
19
6.16
8.5
10
10
6.75
4.5
4.5
0
4.5
3.5
3
1
2
3
4
Recurrences
Epithelial
Stromal
Epithelial + Stromal
Uveitis


Trigger factor
64.7
70
60
50
40
30
20
10
0
No of patients (%)
14.7
8.83
2.94
8.83
1
Trigger factor
Fever
Ocular trauma
Psychological
URI
Spontaneous

S.No	Name	Age	Sex	Initial Pattern	Vision initialy	Vision after treatment	No. of. Recurrences	Pattern of Recurrences				Laterality	Trigger factor	Complication	Disease free interval				Vision after tre recurrer		
								I	II	III	IV				I	II	III	IV	I	II	III
1	Sivanandi	34	M	E	6/24	6/18	1	E				U/L			31				6/18		
2	Pappathi	46	F	E	6/36	6/18	1	E				U/L	Fever		22				6/18		
3	Samykannu	65	M	E	4/60	6/60	1	E				U/L			21				6/60		
4	Pachi	35	F	E	6/36	6/18	1	E				U/L			18				6/18		
5	Saroja	54	F	E	6/60	6/36	1	E				U/L	Ocular trauma		25				6/36		
6	Balan	12	M	E	6/9	6/6	1	E				U/L			14				6/6		
7	Sanbagam	63	F	E	4/60	6/60	1	E				U/L			22				5/60		
8	Muthu	45	M	E	6/36	6/18	1	E				U/L	Stress		27				6/18		
9	Kathamuthu	32	M	E	6/24	6/6	1	E				B/L			33				6/6		
10				E	6/18	6/6	1	E							15				6/6		
11	Karupi	47	F	E	6/36	6/24	1	S				U/L			12				6/36		
12	Kalai	22	M	E	6/18	6/9	1	S				U/L	URI		14				6/12		
13	Podunponnu	42	F	E	6/36	6/18	2	E	E			U/L			24	21			6/24	6/24	
14	Muthukalai	69	M	E	4/60	6/60	2	E	E			U/L		Metaherpetic	21	19			6/60	5/60	
15	Banumathi	35	F	E	6/9	6/6	2	E	S			U/L	Fever		22	16			6/6	6/12	
16	Kalimuthu	37	M	E	6/12	6/6	2	S	S			U/L			19	6			6/12	6/18	
17	Sankar	45	M	E	6/36	6/36	2	S	S			U/L			14	10			6/36	6/60	
18	Stalin	27	M	E	6/12	6/6	3	E	E	E		U/L			19	17	10		6/6	6/9	6/9
19	Savithi	44	F	E	6/36	6/18	4	S	S	S	S	U/L	Fever		16	15	7	3	6/18	6/18	6/24
20	Krishnan	34	M	E	6/18	6/6	4	S	S	S	S	U/L	Ocular trauma		18	15	8	71	6/6	6/9	6/18
21	Musthapa	48	M	S	6/24	6/24	1	S				B/L			10				6/24		
22				S	6/24	6/18	1	S							7				6/18		
23	Santhi	16	F	S	6/18	6/6	1	S				U/L	URI		9				6/6		
24	Pandi	63	M	S	6/60	6/36	1	E				U/L			14				6/36		
25	Meena	18	F	S	6/9	6/6	2	S	S			U/L	Ocular trauma		11	7			6/9	6/9	
26	Murugan	45	M	S	6/36	6/24	2	S	S			B/L			9	4			6/24	6/24	
27				S	6/36	6/24	3	S	S	S				Scarring	4	4	3		6/26	6/60	5/60
28	Senthuram	35	F	S	6/60	6/36	3	S	S	S		U/L	Fever		12	9	17		6/36	6/60	6/60
29	Ganeshan	55	M	S	6/60	6/36	4	S	S	S	S	U/L			8	6	8	4	6/36	6/36	6/36
30	Visalam	50	F	S	6/36	6/24	4	S	S	S	S	U/L		Scarring	10	7	5	5	6/60	6/60	4/60
31	Rajagopal	28	M	S	6/9	6/6	3	E+S	E+S	E+S		U/L			13	8	6		6/6	6/9	6/9
32	Karupayee	43	F	E+S	6/24	6/18	3	E+S	S	S		U/L	Fever	Scarring	9	4	3		6/24	6/36	6/60
33	Thamarai	31	F	E+S	6/36	6/18	4	E+S	E+S	E+S	E+S	U/L			11	8	5	4	6/18	6/18	6/36
34	Sundarapandi	32	M	E+S	6/60	6/24	4	E+S	E+S	E+S	E+S	U/L			10	9	4	3	6/24	6/24	6/24
35	Marutayee	53	F	U	6/36	6/24	3	U	U	U				Glaucoma	12	9	4		6/24	6/36	5/60
36	Kamala	36	F	U	6/60	6/24	4	U	U	U	U	U/L	URI		16	11	5	3	6/24	6/36	6/36
37	Kaliappan	42	M	U	6/60	6/24	3	U	U	E					10	4	3		6/24	6/24	6/24

E- Epithelial k
S- stromal ke
U- Uveitis
U/L - Unilater
B/L - Bilateral

atment in nce
IV
6/36
6/24
6/60
4/60
6/36
6/36
6/60
6/24

keratitis
ratitis

al
l