

CLINICAL STUDY OF VIRAL KERATITISLatha K. S. ¹, Gokila M. S²¹Associate Professor, Department of Ophthalmology, Government Theni Medical College and Hospital, Theni, Tamil Nadu.²Associate Professor, Department of Ophthalmology, Government Theni Medical College and Hospital, Theni, Tamil Nadu.**ABSTRACT****BACKGROUND**

Corneal blindness is a major public health problem in India and the most predominant cause being infectious. Common viral infections include herpes simplex keratitis, herpes zoster ophthalmicus and adenovirus keratitis.

MATERIALS AND METHODS

This study was done in RIOGOH Madras Medical College for 20 months from February 2017 to October 2018.

RESULTS

Out of 100 cases, 56 were primary and 44 were recurrent cases. 55% were in age group of first and second decade. Herpes zoster was commonly noticed after 5th decade. Males affected more than females in the ratio of 1.5:1. Dendritic lesion 42% was the commonest presentation followed by disciform 24%, nummular 7%, punctate 13%, geographic, keratouveitis formed less than 5%. Dendritic lesion yielded the maximum positivity of HSV either with virus isolation or immunofluorescence or both 58%. Total positivity either by virus isolation or HSV antigen detection or by both was 37% showing the importance of clinical diagnosis.

CONCLUSION

HSV infection occupies the major portion of all viral infections followed by adenovirus and HZO. Dendritic lesion was the commonest presentation.

KEYWORDS

Corneal Blindness, Dendritic Lesions Disciform Keratitis, Geographical Ulcer.

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BACKGROUND

Viral keratitis can be classified as herpetic and non-herpetic infections.¹

Herpetic infections- HSV 1 2, HZV, EBV, CMV.

Non-herpetic infections-adenovirus, paramyxovirus, Popova virus, molluscum contagiosum, vaccinia.

Miscellaneous – mumps, measles.

HSV1 generally causes infection above the waist (orofacial and ocular) and HSV 2 is generally sexually transmitted and causes genital infections.

Primary Herpes Infection Pathogenesis

When HSV infects the eye, it replicates in the corneal epithelium and infects the nerve cell ending. The virus reaches the trigeminal ganglion by fast axonal transport and establishes a latent infection in neuronal cells. Reactivation

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of latent virus either from source can result in active viral replication in the corneal epithelium, recurrent infection in corneal stroma or both.

Clinical Features of Ocular HSV**Primary Ocular Herpes**

Primary infection may present as blepharokeratoconjunctivitis. Follicular conjunctivitis may develop. Keratitis develop a few days after conjunctival involvement in 30-50 % of cases.

Geographic ulcer can occur. Subepithelial opacities may develop corresponding to the epithelial lesions and may leave scars. When the stroma is involved the epithelial component of the lesions either heals or desquamate to form filaments, or is cast off or develop into dendritic ulcer.²

Recurrent Infection

The trigger factors are physical or emotional stress or immunosuppression from either endogenous disease or iatrogenic drug management of disease.

Corneal Epithelial Disease

Dendritic Ulcer- this is the most common infection of ocular herpes.

The lesion may begin as discrete punctate epithelial keratitis, then coalesce into dendritic shaped lesion with terminal bulbs.

Pseudo Dendrites

They are much broader with less branching and have no terminal bulbs.

Geographical Ulcer or Amoeboid Ulcer

The dendritic ulcer may broaden or desquamate, forming a large epithelial defect. They have flat edges and stain with rose Bengal viral cultures will be positive. It often follows injudicious use of steroids.

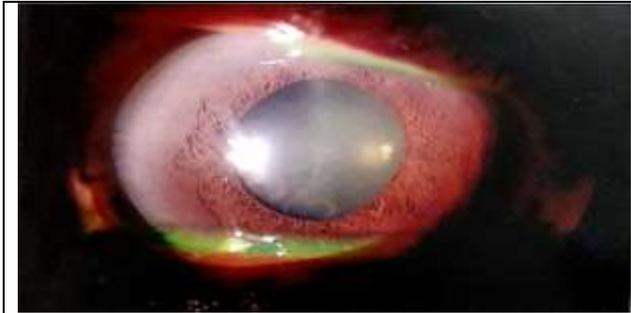


Figure 1. HSV Dendritic Ulcer



Figure 2. Geographic Ulcer

Trophic or Metaherpetic Ulceration

They are generally round or ovoid ulcers with a grey and thickened margin which is due to piled up epithelial cells. These indolent ulcers will take about 12 weeks to repair itself, thus slowing the healing process.

Herpetic Stromal Keratitis²

It may be divided into infectious and immune-

- Infectious disease – necrotising stromal keratitis
- Immune disease (most common form)

Necrotising Stromal Keratitis

It is typically associated with ulceration. It can follow epithelial disease, superficial stromal disease or disciform keratitis. It is due to active viral replication and intense stromal inflammation. It can cause thinning and perforation.

Interstitial Keratitis, Immune Drugs and Limbal Vasculitis

All three forms are antigen antibody complex – mediated disease due to immune complex hypersensitivity.

Disciform Keratitis

This is a central disc shaped corneal opacity with corneal stromal oedema. Keratic precipitates will be seen in the

endothelial surface and Descemet's folds can also occur. Endotheliitis, trabeculitis and secondary glaucoma.



Figure 3. Disciform Keratitis

Management-

1. Clinical Presentation
2. Direct examination of clinical material by
 - a) Light microscopy
 - b) Electron microscopy
 - c) Immune fluorescent microscopy and EIA rapid tests
3. Virus isolation by culture methods
4. Serological diagnosis demonstrating a fourfold rise in antibody titre. ELISA is the test of choice. IgG in serum and secretory Ig A in tears are usually done.
5. Molecular techniques include detection of HSV DNA by polymerase chain reaction

Medical Management³**First Generation Antivirals**

- Trifluridine 1% solution 2 hourly 9 times per day.
- Vidarabine 3 % ointment, 4 hourly 5 times per day.
- IDU 0.5% ointment 4 hourly 5 times a day.

Second Generation Antivirals

Acyclovir 3% eye ointment 5 times per day.

These drugs act by affecting the synthesis of viral DNA and hence less toxic to the host cell.

Surgical Management

Small perforation can be managed by the use of cyanoacrylate glue. If the perforation is large, conjunctival flap may be indicated. After complete healing of the keratitis penetrating keratoplasty can be done. In general, keratoplasty must be done in an uninfamed eye with no deep vascularization in at least less than one quadrant. Use of interrupted fine 10-0 nylon sutures give good results.

Varicella –Zoster Virus Ophthalmicus

Varicella chicken pox and herpes zoster shingles are two distinct clinical diseases caused by the same organism, VZV.

Varicella

It is a primary infection in children from exposure to chicken pox or zoster. Peak incidence in children between 2&6 years of age. Incubation period 10-21 days HZO Trigeminal nerve single most common dermatomal site.

Classic Varicella

Keratitis-

Most common form of epithelial keratitis presents as punctate epithelial keratitis with ground glass appearance usually near the limbus.

Mucus plaque keratitis mostly seen 3-4 months after the onset of cutaneous lesions. It may follow neurotropic keratitis. It will stain with rose Bengal. Virus have never been isolated from mucus plaque keratitis.

Nummular superficial stromal keratitis -they are multiple, ill-defined granular infiltrates of varying size surrounded by stromal haze. Disciform keratitis occurs in 10% of HZO develop within weeks to months.⁴

Neuroparalytic Ulceration can occur.

Diagnosis

Diagnosis is made by characteristic pain and appearance of the dermatomal rashes more often than not lab tests are unnecessary.

Confirmatory Lab Tests

1. Morphologic Test

Tzanck smear –typical findings of multinucleated giant syncytial cells and acidophilic intranuclear inclusion bodies will be seen.

2. Immunologic Tests

- Immunofluorescence
- Radio immune assay
- ELISA
- Agar gel immunodiffusion

3. Serological Tests for Antibodies

- Neutralising antibody test
- ELISA
- RIA
- Membrane antigen IF
- Immune adherence hemagglutination⁵

Treatment

For herpes zoster epithelial keratitis topical acyclovir ointment 3% 5 times per day can be tried. Mainstay of therapy is systemic acyclovir.

Current dosage for oral acyclovir is 800 mg 5 times / day for 10 days starting within 72 hours of the onset of skin lesions. Topical steroids and cycloplegics may be used for stromal, disciform keratitis or uveitis resulting in pain or decreased vision. Post herpetic neuralgia may respond to capsaicin 0.25% skin ointment twice daily. Tricyclic antidepressants may be useful for post herpetic neuralgia. Neurotrophic corneal epithelial defects can be treated with non-preserved lubricants, bandage contact lens or tarsorrhaphy.

Other Herpetic Infections

Ebstein Bar Virus

It is the most common cause of acute dacryoadenitis. Acute follicular conjunctivitis, Parinaud's oculoglandular syndrome, have been reported in acute infections.

It can cause multiple corneal epithelial dendrites involving central or peripheral cornea. Multiple granular ring shaped or nummular opacities in anterior midstroma can occur mid to deep peripheral infiltrates with vascularisation.

Management

EBV stromal keratitis is generally self-limited.

Topical steroids indicated in patients with significant reduction of vision.

Non-Herpetic Viral Infection

Adeno Viral Keratitis

Adeno virus are the most common cause of acute viral infection of external eye and cornea.

EKC- epidemic keratoconjunctivitis

PCF – pharyngoconjunctival fever

Serotypes are 8, 11, 12, 19 most common strains.

Adenovirus keratitis has sequelae of superficial epithelial keratitis, deep epithelial and sub epithelial keratitis. PCF manifests as an acute follicular conjunctivitis with associated URTI and fever. PEK and subepithelial infiltrates are less common.

Molluscum Contagiosum

It can produce umbilicated nodule on eyelid margin. It can also develop chronic follicular conjunctivitis, PEE, superficial vascular pannus on the cornea.

It is a self-limiting disease. Treatment involves complete excision of the nodule.

Objectives of the Study

1. To assess the epidemiology of viral keratitis namely herpes simplex keratitis, herpes zoster ophthalmicus, adeno viral keratitis.
2. To evaluate the clinical features in viral keratitis.
3. To correlate microbiological investigations with clinical features.

MATERIALS AND METHODS

This study was done in regional institute of ophthalmology and government ophthalmology hospital, madras. Duration of the study was 20 months from the February 2017 to October 2018.

Inclusion Criteria

1. Epithelial involvement like superficial punctate epithelial keratitis, nummular keratitis, dendritic or geographical ulcer
2. Stromal keratitis like disciform and necrotising keratitis
3. Keratouveitis

Exclusion Criteria

Patients with only viral conjunctivitis and vesicular lid lesions were not included in the study

Clinical Evaluation

History

A detailed history was taken regarding symptoms, duration of illness and any predisposing factors like fever, URTI, trauma, exposure to intense heat, mental stress, menstruation and drug intake.

Patients were enquired about past history of similar illness, and any history of application of antivirals and steroids.

Local Application

Corneal sensation was tested in all cases and visual acuity was recorded. Epithelial lesions were stained with double staining using 1% rose Bengal and 2% fluorescein.

Patients were grouped into primary and recurrent cases depending on their history, clinical features and treatment patient has had on earlier episode. Each case was followed up for 3 months. After application of 4% xylocaine topically, corneal scrapings were taken with Bard Parker blade. The material was put into a test tube containing viral transport medium Hanke's BSS or minimum essential medium and taken to microbiological investigations.

The cell culture was done in Vero cell line using monkey kidney cell line. The culture was observed for cytopathic changes, like loss of elongated or prolonged shape of normal cell and replacement by refractile round cells. The cell line also showed ballooning of cells and plaque formation. The changes began in discrete foci or several foci and progressed to include the entire cell line. The culture was observed for 2 weeks before discarding them as negative.

Corneal scrapings taken on a fresh slide was fixed with methanol. The slide was used for immune fluorescence using anti- rabbit IgG. The presence of an apple green

fluorescence under fluorescent microscope was taken as positive evidence of viral antigen.

For detection of antibody, blood samples were taken on first day and after 2 weeks and examined for rise in antibody titre. Measurement of anti HSV IgG was done by solid phase ELISA using HSV antigen prepared from tissue culture. A fourfold rise in titre was considered as significant.

RESULTS

Incidence

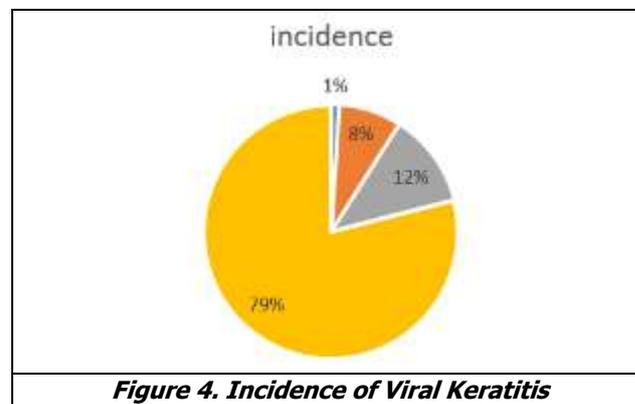


Figure 4. Incidence of Viral Keratitis

Out of 100 cases, HSV keratitis 79 cases, adenovirus 12 cases, HZO 8 cases, keratitis due to chicken pox 1 case.

The cases were grouped into primary and recurrent depending on clinical picture and history.

Total No. of Cases	100
Primary	56
Recurrent	44

Table 1. Primary and Recurrent Cases

Age Group

The youngest patient in the study was 4 years old. Patients age ranged from 4-70 years.

Age in Years	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Primary	6	21	20	4	1	2	2	-
Secondary	1	4	10	6	4	7	1	1

Table 2. Age Group of Patients

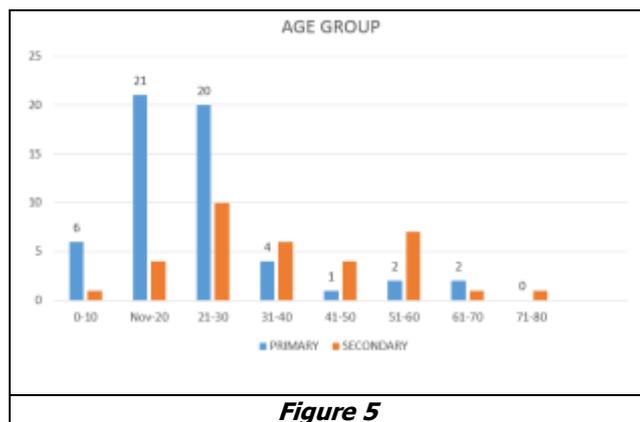


Figure 5

Maximum number of cases (55%) belonged to patients in first to second decade

Sex

	Males	Female
Primary	37	22
secondary	24	17

Table 3. Sex Group of the Patients

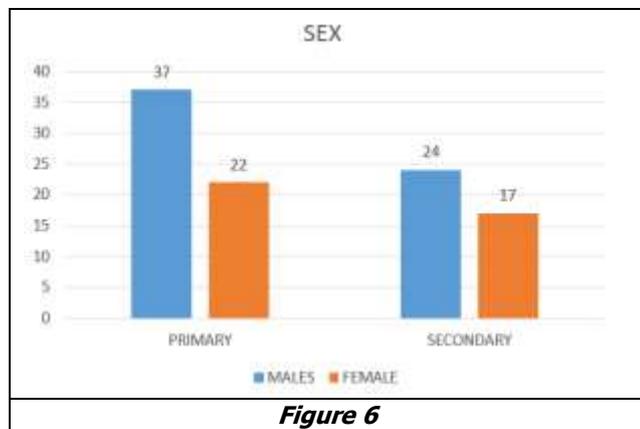


Figure 6

Both in primary and recurrent, the ratio of males to female was 1.5:1

Laterality

Bilateral Cases	
Total	12
Recurrent	3
primary	9

Table 4. Laterality

Out of 12 cases, 9 were primary and 3 were recurrent

Seasonal Variation

A seasonal variation was noted statistically with the number of cases more in the period of May to September.

Associated Systemic Illness

	Primary	Recurrent	Total
Fever	30	24	54
H. labialis	20	10	30
rhinitis	3	2	5

Table 5. Associated Systemic Illness

Triggering Factor	Recurrent Cases
	Number of %
Fever	12
Trauma	7
Excessive Exposure to Sun	3
Rhinitis	3

Table 6. Triggering Factors

Fever was the commonest precipitating factor in 12 patients, 7 patients gave definite history of injury as triggering factor. URTI and excessive exposure to sun was present in 6 cases. In the remaining 19 cases no specific cause could be traced.

Recurrence Rate

The number of recurrent herpetic attack varied from thrice a year to one attack in 6 years average being 1.5 years

Symptoms

Commonest symptoms were photophobia and watering

Duration of Symptoms

Duration in Days	No. of Patients
0-5	16
6-10	27
11-14	15
>2 weeks	42

Table 7. Showing Duration of Symptoms

Most of the patients reported only after onset of the symptoms to the hospital. Only 16% of patients reported within 5 days and 42% of patients reported in 2nd week.

Clinical Features of Viral Keratitis

	Primary	Recurrent	Total %
Punctate	1	1	2
SPK	7	6	13
Nummular	3	4	7
dendritic	20	19	39
Geographic	3	-	3
Keratouveitis	4	1	5
Stromal with epithelial	-	2	2
Disciform	12	12	24
Pseudodendrite	1	-	1
diffuse	2	2	4

Table 8. Clinical Features of Viral Keratitis

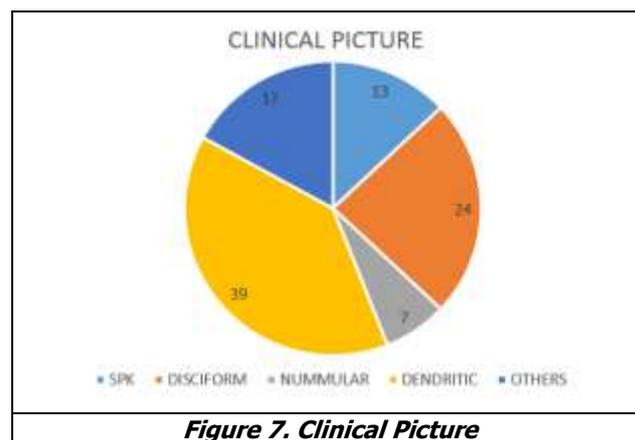


Figure 7. Clinical Picture

Dendritic keratitis (39%) followed by disciform keratitis (24%) is the most common clinical features seen.

Positivity of Lesions

Lesions	Positivity %
SPK	40
Dendrite	58
Geographic	66
keratouveitis	30

Table 9. Positivity of Lesions

58% of dendritic lesions and 40% of punctate lesions showed positivity either by virus isolation or by antigen detection or by both.

HSV Lab Analysis

	Culture Alone Positive	If Alone Positive	Both Positive	Both Negative
Primary	10	14	6	10
Recurrent	3	12	3	11
Total	13	26	9	21

Table 10. HSV Lab Analysis

Virus isolation was found to be positive in 16 primary cases and 6 recurrent cases. So total culture positivity is 22 cases (27%).

Immunofluorescence was positive in 20 primary and 15 recurrent cases. Total positivity being 35 cases 44%.

Primary infection showed a positivity of 30 cases (37%) and recurrent 18 cases (22%).

Analysing the data of HSV virus isolation and antigen detection by immune fluorescence technique, virus isolation was found to be positive in 16 primary cases and 6 recurrent cases. So total culture positivity is 22 cases (27%).

Immunofluorescence was positive in 20 primary and 15 recurrent cases. total positivity being 35 cases 44%.

Primary infection showed a positivity of 30 cases (37%) and recurrent 18 cases (22%).

Analysing the data of 12 adenoviral cases, 6 cases (50%) showed positivity of viral isolation and immunofluorescence. in herpes zoster keratitis out of 8 cases, 2 cases (25%) showed positivity of viral isolation and immunofluorescence.

Serological Diagnosis

41 paired sera were tested for HSV, adenovirus antibody estimation, which demonstrated positivity in all samples. However, four-fold rise in titre was seen only in 9 cases of 38 paired sera and out of this 8 were primary and 1 recurrent.

DISCUSSION

100 cases were clinically diagnosed as viral keratitis due to HSV, HZO, adenovirus, varicella during the study periods of 20 months. Cases included for study were epithelial, stromal keratitis, as well as keratouveitis.⁶ Cases with only lid with conjunctival lesions were not taken up for study

Cases were grouped into 56 primary 44 recurrent cases⁷ based on their history clinical features and the treatment patient has had on earlier episode.

Age Group

The age group of study ranged from 4 years to 70 years. 50% of patients belonged to first to third decade HSV infection is found to be less in young children now.

Sex

Our study demonstrates male predominance with a ratio of 1.5:1 both in primary and recurrent infection.

Laterality

Bilateral cases seen in most of adenoviral infections.

Clinical Picture

Dendritic lesions 42% was the commonest presentation. Followed by disciform 24%, nummular 7%, punctate 13%, geographic, keratouveitis formed less than 5%

Dendritic lesions yielded the maximum positivity of HSV either with virus isolation or immunofluorescence or by both 58%. The SPK 40%, geographic 66%, keratouveitis 30%.

In HSV total culture positivity is 22 cases (27%). Immunofluorescence⁸ positivity is 35 cases (44%) were positive either by the above 2 methods or both. In adenovirus positivity is 50%. In HZO positivity is 25%. Presence of interferon and antibodies and absence of viable particles for CPE changes in cell culture are the reasons for their low positivity. This shows the importance of clinical diagnosis, since almost all cases responded to antivirals.

CONCLUSION

HSV infection is the commonest of all viral infections followed by adenovirus and HZO. 55% of the patients belonged to first and second decade. Herpes zoster infection was commonly noticed after 5th decade. Males were more affected than females in a ratio 1.5: 1. Bilateral cases were common in adenoviral infection. A seasonal variation with maximum number of cases in May to September was noted. Fever was the commonest triggering factor followed by trauma. Number of recurrences varied from thrice a year to once in 6 years with a mean of 1.5 years in HSV infection. Dendritic lesion was the commonest presentation and also maximum positivity was noted with the same lesion. Total positivity either by virus isolation or HSV antigen detection or by both was 37% showing the importance of clinical diagnosis.

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