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Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. Ron Melton and Dr. Randall Thomas entitled **Herpes Simplex Viral Keratitis.** In order to obtain 2-hours of COPE-approved CE credit, please refer to page 254 for complete instructions.

Herpes Simplex Viral Keratitis

Ron Melton, OD; Randall Thomas, OD

Subjective

A 65-year-old white woman presents with an increasingly irritated right eye for the past four days (Fig. 1). She is currently under chronic care for her advanced dry eye syndrome. She uses preservative-free (PF) artificial tears inconsistently for her ocular surface disease.

Objective

- 2+ conjunctival injection OD, 1+ OS
- 2+ Rose Bengal staining OU
- Multiple dendriform lesions of the superior corneal epithelium OD (Fig. 2)

Assessment

- Epithelial herpes simplex keratitis (HSK) OD
- Bilateral keratoconjunctivitis sicca

Plan

- Viroptic (trifluridine) ophthalmic solution 1 gt. OD q.2h. x 4 days
- Soothe (emollient lubricant by Alimera Sciences) q.2h. OU x 4 days
- Alternate the drops allowing for instillation of an eye drop every hour
- Return to clinic in 4 days

First Follow-Up Visit

Subjective

- OD feels much better

Objective

- Herpetic lesions 80% improved

Assessment

- HSK responding nicely to antiviral therapy

Plan

- Decrease Viroptic to q.i.d. OD x 4 days
- Continue Soothe q.i.d. OU x 4 days
- Return to clinic in 4 more days

Second Follow-Up Visit

Subjective

- Both eyes feel "much better"

Objective

- Corneal epithelium renormalized OD
- BUT is 6 to 7 seconds OU
- Modest reduction in Rose Bengal staining pattern

Assessment

- Resolved HSK
- Chronic keratoconjunctivitis sicca with chronic ocular surface disease

Plan

- Discontinue Viroptic
- Continue Soothe q.i.d OU long-term to provide ocular surface protection
- Re-evaluate patient in one month to assess ocular surface status. At that time, decide whether to modify topical therapy and/or insert punctal plugs or consider Restasis.

Comments: This rather straightforward diagnosis is complicated by the underlying dry eyes. Since all topically applied antivirals are toxic to the cornea, or certainly have that potential, concurrent use of artificial tears is useful when treating HSK. Because this patient had pre-existing keratoconjunctival epithelial tissue compromise, it was important to use an artificial tear which provides significant protection to the ocular surface. Soothe is a newer artificial

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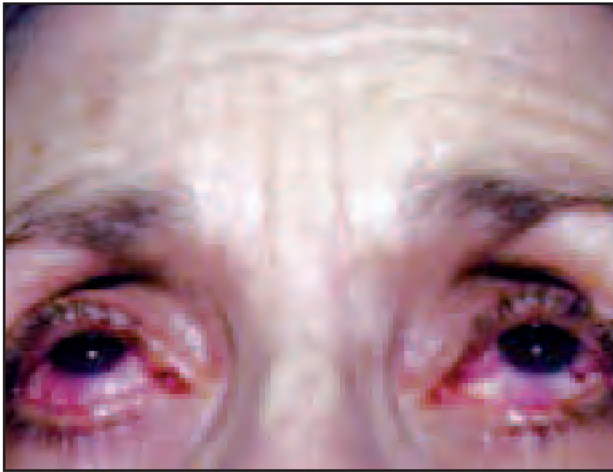

Fig. 1 While it is obvious that this woman has severe dry eyes, as evidenced by Rose Bengal staining, her chief complaint was that her right eye was hurting.

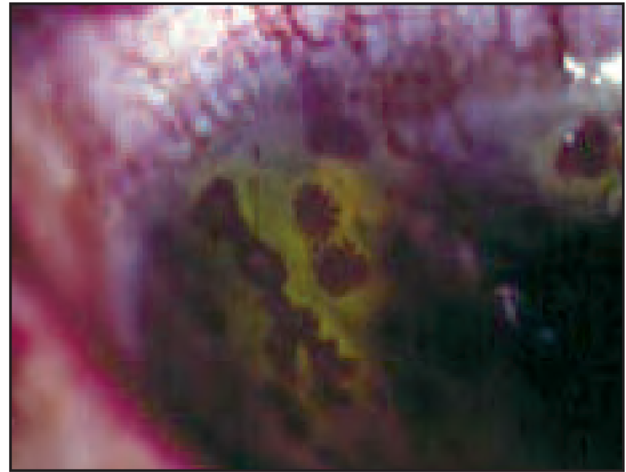

Fig. 2 Upon more careful inspection of her right cornea, it can be seen that she has classic herpes epithelial keratitis.

tear that is a meta-stable emulsion. It rapidly provides a protective lipid barrier and replenishes the complete tear film. It is available in a 15 mL bottle by Alimera Sciences out of Atlanta, Georgia.

Advise the patient that there is a 25% to 50% chance of HSK recurrence and to return promptly if the symptoms reappear. Timely, proper therapy usually results in little or no scarring. (Note: While Viroptic is properly stored in refrigeration, once the drug is dispensed to a patient, it does not have to be kept refrigerated.)

General Overview

- About 50,000 new cases each year
- Leading cause of corneal opacification
- Common cause of unilateral red eye with tearing, photophobia, irritation, and sometimes decreased vision
- Fellow eye is not at risk to develop infection
- History of cold sores/fever blisters is occasionally helpful in diagnosis
- About 90% of adults harbor this neurotrophic virus following a usually asymptomatic primary infection as a child
- Latent virus resides in gasserian (trigeminal) ganglion
- Two common types: I and II, of which type II is usually genital
- Opportunistic virus reactivation risk factors: fever, stress, menstruation, sunburn, trauma, corticosteroid use, adrenergic or prostaglandin eye drops, or any immuno-compromising condition
- Following the first secondary (epithelial) infection, there is about a one in four chance of another recurrence. Following a second recurrence, the chance of another recurrence is about 40% to 45%. Males tend to have recurrence a bit more than females.
- The genome, or DNA uniqueness, of the various herpes strains is thought to direct the clinical behavior and clinical expression of the infecting virus: i.e., end-bulbs vs. bifurcations and branches without end-bulbs, serious vs. mild pathogenicity, causing stromal disease vs. nonstromal involvement, steroid exacerbation of disease vs. non-steroid exacerbation, etc.
- Factors that complicate and prolong the natural history and clinical management:
  - Infectious foci near the limbus
  - Prior treatment with corticosteroids
  - Delay in seeking care by the patient
  - Underlying stromal inflammation

Clinical Observations: Epithelial Disease

- Cornea may initially show coarse, punctate, SPK-like lesions which usually coalesce to form linear or dendritiform appearance (Fig. 3), or less commonly, a geographic lesion
- Hypoesthesia to the affected cornea (Q-tip sensitivity test can occasionally be helpful)
- Pain not usually severe because of subdued corneal afferent neuronal sensitivity (via the nasociliary pathway)
- Fluorescein tends to stain the central ulcer bed, whereas Lissamine Green or Rose Bengal tends to stain the devitalized tissues at the leading edges of viral proliferation

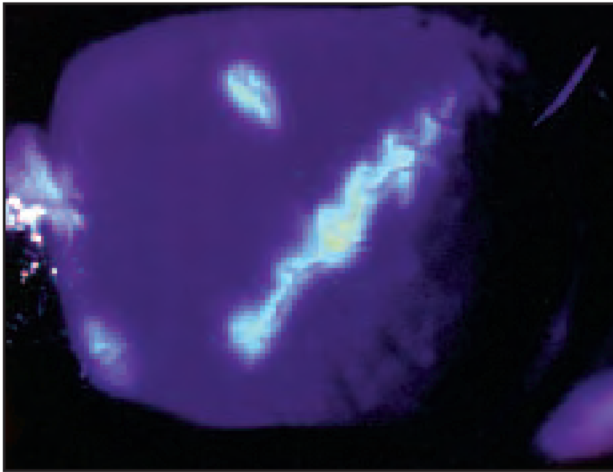

Fig. 3 Classic herpes simplex epithelial infection

Medical Management of Epithelial Disease

- Viroptic solution — one drop every two hours (not to exceed 8 to 9 times a day) until the epithelial lesion is mostly healed, usually 4 to 7 days, then usually 4 to 5 times daily for 4 to 7 more days. Once re-epithelialization is largely achieved and the frequency of Viroptic is reduced, consider adding preservative-free artificial tears every hour or two in between the Viroptic drops. Adding such therapy to any medical treatment is helpful in re-establishing corneal tissue integrity.
- If the patient becomes allergic to Viroptic, switch to an oral antiviral.
- Or mechanically debride the infected corneal epithelium and patch over erythromycin ointment much as one would patch over a corneal abrasion. It may take 2 or 3 days of patching to achieve healing.
- Always cycloplege (usually with 5% homatropine) if there is any significant corneal involvement or anterior chamber reaction.

Clinical Observations: Stromal Disease

- Stromal involvement, when it does occur, can significantly complicate the management of herpetic keratitis
- Even minor stromal involvement can retard the rate and quality of re-epithelialization
- Seen in about one fifth of cases and can be concurrent, but is usually delayed weeks or months after an episode of epithelial disease
- Focal stromal opacification is a critical slit lamp finding. This usually occurs beneath the epithelial lesion (or where the epithelial lesion was located)
- Stromal inflammatory disease can be antigen-antibody-complement-mediated and/or delayed, cell-mediated (lymphocyte-plasma cell) hypersensitivity in nature; both of which are generally steroid responsive
- It is the judicious use of topical corticosteroids, initially along with topical antiviral coverage, that is critical in the management of active stromal disease. Once the frequency of topical corticosteroid drops is tapered to two or three instillations per day, it is usual to stop or taper the antiviral coverage.
- Once the stroma becomes involved, a mild secondary iridocyclitis is a common accompaniment and is managed largely via cycloplegia.
- Tapering the topical corticosteroid eye drops usually is a long, tedious process often taking many weeks to many months. For this reason, loteprednol is the steroid of choice. Most patients have to maintain q.d. or q.o.d. administration indefinitely.
- Once the active stromal inflammation is under control, use of a long-term, low-dose oral antiviral should be considered. Likewise, patients with frequent recurrences of epithelial disease (with or without stromal involvement) may benefit from similar therapy. Options are: Acyclovir 400 mg b.i.d., Valtrex 250 b.i.d., or Famvir 125 mg b.i.d.

Disclaimer: Not every detail of every case is discussed, rather the key clinical findings are described. For example, if nothing is said about the corneal status, you should assume that the cornea is normal, etc. When vision is recorded, it should be assumed to be best corrected or pinholed. Regarding therapy, we show how we treated the particular case. Given that medicine is an art, as well as a science, therapy will — and often does — vary with each unique patient presentation depending on severity, known drug allergies, prior treatment, response to therapy, etc.

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QUESTIONNAIRE

Herpes Simplex Viral Keratitis

Ron Melton, OD; Randall Thomas, OD

1. Which of the following statements does **NOT** describe the patient at initial presentation?
   - ❏ Multiple dendriform lesions of superior corneal epithelium OD
   - ❏ History of intermittent pain in right eye for past 5 years
   - ❏ 2+ Rose Bengal staining OU
   - ❏ 2+ conjunctival injection OD, 1+ OS

2. Identify the **FALSE** statement regarding the patient's treatment plan:
   - ❏ Viroptic (trifluridine) ophthalmic solution 1 gt. OD q.2h. x 4 days
   - ❏ Soothe (emollient lubricant) q.2h. OU x 4 days
   - ❏ Follow-up in 4 days
   - ❏ None of the above

3. Which of the following statements does **NOT** describe the patient and her assessment at first follow-up?
   - ❏ Herpetic lesions 80% improved
   - ❏ Diminished pain OD
   - ❏ HSK responding nicely to antiviral therapy
   - ❏ Diminished pain OS

4. All of the following statements describe the patient at second follow-up, **EXCEPT**:
   - ❏ BUT 6 to 7 seconds OD and BUT 15 seconds OS
   - ❏ BUT 6 to 7 seconds OU
   - ❏ Corneal epithelium renormalized OD
   - ❏ Modest reduction in Rose Bengal staining pattern

5. All of the following statements about herpes simplex keratitis (HSK) are true, **EXCEPT**:
   - ❏ A key presenting symptom is pain
   - ❏ It is usually accompanied by significant mucous discharge
   - ❏ Topically applied antivirals are toxic to the cornea, or have the potential to be
   - ❏ Ocular surface protection was considered in this case because of keratoconjunctival epithelial tissue compromise

6. Which of the following statements about HSK is **FALSE**?
   - ❏ Incidence is roughly 50,000 new cases per year
   - ❏ It is the leading cause of corneal opacification
   - ❏ The fellow eye typically becomes infected, even in mild cases
   - ❏ Latent virus resides in gasserian (trigeminal) ganglion

7. HSK is a common cause of which of the following?
   - ❏ Unilateral red eye
   - ❏ Tearing
   - ❏ Photophobia
   - ❏ All of the above

8. Which of the following statements about incidence of HSK recurrence is **FALSE**?
   - ❏ 25% to 50% chance
   - ❏ 10% to 25% chance in patients <25 years of age
   - ❏ Higher in Asian population
   - ❏ All of the above

9. All of the following are opportunistic virus reactivation risk factors, **EXCEPT**:
   - ❏ Onset of menopause
   - ❏ Menstruation
   - ❏ Sunburn
   - ❏ Corticosteroid use

10. Which of the following statements about recurrence is **FALSE**?
    - ❏ Following first epithelial infection, one in four chance of second recurrence
    - ❏ Following second recurrence, 40% to 45% chance of recurrence
    - ❏ Higher incidence in males than in females
    - ❏ Occurs more frequently in females

11. Which of the following factors influences the natural history and management of HSK?
    - ❏ Patient delay in seeking care
    - ❏ Infectious foci near the limbus
    - ❏ Prior use of corticosteroids
    - ❏ All of the above

12. Identify the **FALSE** statement regarding epithelial disease:
    - ❏ Cornea may show a geographic lesion
    - ❏ Hypoesthesia to the affected cornea may be present
    - ❏ Fluorescein staining usually to the central ulcer bed
    - ❏ Usually accompanied by severe pain

13. Which of the following statements does **NOT** describe Soothe artificial tears?
    - ❏ Meta-stable emulsion
    - ❏ Protects ocular surface
    - ❏ Is effective but slow-acting
    - ❏ Replenishes complete tear film

14. In the medical management of epithelial disease, which of the following is recommended?
    - ❏ Viroptic solution: one drop every two hours until significant healing
    - ❏ Following reduction of Viroptic dosage, preservative-free artificial tears
    - ❏ Cycloplege if significant corneal involvement or anterior chamber reaction is present
    - ❏ All of the above

15. If a patient is allergic to Viroptic, which of the following measures is recommended?
    - ❏ Switch to an oral antiviral
    - ❏ Continue treatment until patient builds up tolerance to the product
    - ❏ Mechanically debride the infected corneal epithelium
    - ❏ Patch over erythromycin ointment as if patching a corneal abrasion

16. Which of the following statements about stromal disease is **FALSE**?
    - ❏ It can complicate the management of herpetic keratitis
    - ❏ It can affect re-epithelialization
    - ❏ An oral antiviral is recommended as soon as active stromal inflammation is detected
    - ❏ Treatment comprises judicious use of topical corticosteroids

17. Which of the following is recommended to help reduce recurrences of epithelial and stromal herpetic disease?
    - ❏ Acyclovir 400 mg b.i.d.
    - ❏ Valtrex 250 b.i.d.
    - ❏ Famvir 125 mg b.i.d.
    - ❏ All of the above

18. Which of the following statements regarding stromal inflammation is **TRUE**?
    - ❏ It is best treated with corticosteroids, combined initially with topical antiviral coverage
    - ❏ Mild secondary iridocyclitis commonly accompanies stromal involvement
    - ❏ Loteprednol is a steroid of choice because of its safety profile
    - ❏ All of the above

19. All of the following statements about HSK are true, **EXCEPT**:
    - ❏ It is a common cause of photophobia
    - ❏ It is a common cause of dry eye syndrome
    - ❏ History of cold sores is occasionally helpful in diagnosis
    - ❏ About 90% of adults harbor the neurotrophic virus following a usually asymptomatic primary infection in childhood

20. Which of the following statements about HSK is **FALSE**?
    - ❏ The genome of the various herpes strains may direct the clinical expression of the infecting virus
    - ❏ Delay in seeking care is not a factor in successful treatment
    - ❏ Underlying stromal inflammation may complicate its management
    - ❏ Infectious foci near the limbus may prolong the natural history of the disease