HERPETIC KERATITIS: A REVIEW AND WHAT'S NEW

Dr Douglas Rett OD, FAAO
DoctorRett@gmail.com

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IMPORTANCE OF STUDYING HERPES

- Herpes viruses are globally ubiquitous and non-discriminatory to race or gender
- Over the last generation, vaccines have changed the presentation of herpes zoster, and have the potential to do so even more in the near future.
- Herpes simplex eye disease is a major cause of blindness worldwide.
- Patients with herpetic symptoms often first present to eye care providers before any other health care is sought.
LECTURE OUTLINE

- VZV → HZV
  - Signs of systemic disease and how vaccines play a role
- HZK
  - Signs of ocular disease and how to differentiate
- HSV
  - Signs of localized disease
- HSK
  - Signs of ocular disease and how to treat
POLL QUESTION #1

How comfortable are you with managing herpetic eye disease?

1. Not Comfortable at all
2. Slightly comfortable but need to know more
3. Comfortable/OK
4. Very Comfortable
ETYMOLOGY

- Hippocrates practiced medicine around 400BC and described a cluster of vesicles as ‘herpes’: Greek for “crawling/spreading”
- The Greek word ‘zoster’ describes a girdle worn over half the body (red for warriors)
- Varicella is from the Latin meaning “pock” or “pustule”
- Simplex is also Latin meaning “single”
VARICELLA-ZOSTER VIRUS

- **VZV=Chicken Pox (primary infection)**
- **HZV=Shingles (reactivation of latent VZV)**
- Highly contagious typically via respiratory transmission
- 50% of cases are children 5-9
- 1-4d of prodromal low-grade fever and malaise → Papular rash → vesicles for 4d
- Most common complication
  - In youth
    - Bacterial superinfection
  - In adults
    - Pneumonia

Healthline.com
HERPES ZOSTER VIRUS

- Reactivation of latent VZV within sensory ganglia
- Can happen at any age, but typically over 50yo
- Recurrent zoster in an immunocompetent patient is rare
- Not usually recent exposure to VZV infection
- Rash starts as erythematous papules → grouped vesicles
  - Usually limited to one dermatome
  - Crust by one week
- Pain is common
  - Can be prodromal
  - “Burning”
  - “Stabbing”
  - “Throbbing”
POST-HERPETIC NEURALGIA

• Most common complication of HZV is Post-Herpetic Neuralgia
  – Refers to pain persisting beyond 4mo from onset
  – Can be exquisitely painful
  – 10-15% of all HZV pts
  – 50% of PHN pts are over 60yo
  – Reduced quality of life; physically and psychologically
POLL QUESTION #2

Which branch of the Trigeminal Nerve is most commonly affected in Herpes Zoster?

1. V1
2. V2
3. V3
4. V4
Zoster Distribution

V1 is most commonly affected

V1 Branches: Frontal (most affected), Lacrimal, Nasociliary (globe)
Specifically when the reactivation is along the V1 distribution
Typically vesicles on eyelid(s), non-specific conjunctivitis
10-20% of all HZV involves V1
Nasociliary nerve innervates: Ethmoid sinus, both eyelids, top of nose, essentially all of globe
  - Hutchinson’s sign:
    • Not a great prognosticator; more of a caution
    • If vesicles on nose (tip?), then globe is involved.
Periocular skin and lids
  - Starts as edema, then itch, pain, papular rash->vesicles
Conjunctiva
  - Vesicles are possible but most just hyperemia
Episcleritis/scleritis
LIDS AND OCULAR SURFACE

Day 1: Headache and skin itch

Day 2: “excruciating” skin pain
Day 4: burning pain, swollen eye

Day 7; conj, cornea, uvea & retina involvement
HZO CORNEA

- Punctate Epithelial Erosions (PEEs) most common sign
- Pseudodendrites: thought to represent coalescence of old PEEs
  - Differ from HSK as more superficial, stain minimally, have blunt ends (no end-bulbs)

Dr. Trevor Gray
HZO CORNEA CONT.

- Infiltrates: anterior stromal, underlying PEEs, nummular (coin)
- Keratouveitis/endotheliitis: corneal edema and keratic precipitates (KPs) and uveitis (1wk into disease course)
- Disciform Keratitis and uveitis: not as common as in HSK (will discuss later)
ZOSTER MANAGEMENT
WE CAN PREVENT/SLOW:

- **VZV**
  - Chickenpox is responsible for:
    - Scarring from super-infection
    - Death from pneumonia or encephalitis
      - In the 80s, each year: 3 million cases; 11,000 hospitalizations; 100 deaths
      - Higher risk if HIV or kids taking steroids for asthma
      - Adults 40x higher risk of death than kids
    - Death from perinatal varicella
      - Maternal infection right before/after birth

- **HZV**
  - Shingles is responsible for:
    - Average of 12d missed work

- **PHN**
  - PHN is responsible for:
    - Average of 12d hospitalization
    - Most common cause of suicide in patients with chronic pain over 70y
VARICELLA VACCINATION

• US first started varicella vaccination in 1995
  – Was one dose (IM)
  – 80% effectiveness in preventing ANY varicella
  – 95% effectiveness in preventing hospitalization
• Switched to combo with MMR
  – Two doses (IM) @ 12mo and @4-6yrs
  – 95% effectiveness in preventing ANY varicella
• In 2014, adolescents in US
  – 95% have received one dose
  – 81% have received two doses
• As compared to the early 1990s (in US):
  – Varicella deaths declined 87%
  – Varicella hospitalizations declined 93%
SHINGLES VACCINATION

- **Zostavax**
  - zoster vaccine live, Merck
- **Shingrex**
  - zoster vaccine recombinant, adjuvanted, GSK

- Both work by boosting the cell-mediated immune response
POLL QUESTION #3

Around which year did the first major Herpes Zoster vaccine become available?

1. 1986
2. 1996
3. 2006
4. 2016
VACCINE DETAILS

• Zostavax came out first in 2006
  – Needs just one dose (IM)
  – Recommended in people over 60
• Shingrix came out in 2017
  – Needs two doses (IM)
  – Recommended in people over 50

• Large studies show Shingrix more effective and for more years
• CDC recommends all adults over 50 get Shingrix

• One in Three Humans will get Shingles
HERPES SIMPLEX
HERPES SIMPLEX

- Completely different virus (Human Herpes Virus 1+2)
- HSV-1 accounts for most oral, labial and ocular infections
- HSV-2 accounts for most genital infections

- Infection follows direct inoculation of mucosal or skin surfaces
- Latency develops after virus enters sensory neurons and travels to sensory ganglia
HSV SKIN INFECTION PATHOGENESIS

- Most ocular disease is a reactivation, not primary infection
  - Triggers: stress, fever, sunlight, hormonal changes
- More localized in comparison with VZV
- More than 90% of adults have antibodies to HSV-1 by 40yo
HSK EPIDEMIOLOGY

• More than 90% are unilateral; recurrences affecting same eye
• Recurrence rates:
  – 9% after one year
  – 23% after two years
  – 67% after ten years
HSK PATHOPHYSIOLOGY

• 3 problems:
  – 1. Active infection
    • Reactivated virus enters cells
    • Cells die
  – 2. Inflammation from active infection
    • Inflammatory cytokines break down cells and ruin clarity
  – 3. Immune reaction from past infection
    • Retained viral antigens stimulate inflammation

• Keep in mind that each level of the eye can have each problem!
HSK DIAGNOSIS

- Typically made on clinical appearance alone
- Can culture
  - Takes at least 1-2d; but ELISA or PCR faster
- Serologic testing not helpful d/t ubiquity

- DDx!!!!
HSK CATEGORIES

1. Epithelial Keratitis
2. Stromal Keratitis
3. Endotheliitis
4. Neurotrophic keratitis

- Can also affect eyelids, conjunctiva, retina and sclera
  - But Cornea is most prevalent (more nerve endings?)
EPITHELIAL HSK

- Most frequent form of HSK
- Dendritic or geographic ulcers
- Untreated disease averages 17d
  - Recurrences average 28d
- Symptoms: photophobia, pain, watery discharge
- Signs:
  - Early: PEEs $\rightarrow$ tiny, clear vesicles
  - 2nd 24hrs: Vesicles $\rightarrow$ Dendrites
- Dendrite is a “True ulcer” in that it can extend through the basement membrane
EPITHELIAL HSK
DENDRITE EPITHELIOPATHY

• Abnormal epi persists weeks after the dendrite has healed
GEOGRAPHIC EPITHELIAL HSK

- 22% of epithelial HSK
- Longer duration of symptoms and time to heal
- More associated with previous topical steroid use
STROMAL HSK

• Primary stromal infection
  – Approximately 2% of HSK cases
• Secondary stromal involvement
  – 2^ Infectious epi HSK
  – 2^ Infectious endo HSK
  – 2^ Neurotrophic HSK

• Regardless, scarring in stromal must be minimized and treatment focused on the cause of stromal involvement
Necrotizing Stromal HSK

- Term for direct viral infection of the stroma
  - Most rare of the 3 types of stromal involvement
- Signs:
  - Dense infiltrate with overlying epi defect
  - Stromal thinning
- Mechanism of tissue destruction:
  - Replicating virus
  - Severe host inflammation
- Can lead to perforation quickly
NECROTIZING STROMAL HSK
IMMUNE STROMAL (INTERSTITIAL) KERATITIS

- Occurs as a recurrence of HSK
  - Days to years after epi HSK
  - Up to 20% of all HSK
- Cell-mediated delayed hypersensitivity to viral antigens in K
- Signs:
  - Intact epi
  - Stromal infiltrate
    - Punctate or diffuse
  - Stromal neovascularization
    - Brings scarring (immune reaction) and thinning (cytokines)
IMMUNE STROMAL HSK
ENDOTHELITIS

- Inflammatory reaction at the level of endothelium
  - Not true infection
- Signs: Stromal edema without infiltrate, KPs and iritis
- Often in disciform shape

- What separates it from normal iritis:
  - K edema
e  - High IOP
  - Likely $2^\text{trabeculitits}$
  - KP debris in AC
NEUROTROPHIC HSK

- Neither immune nor infectious
- Hypesthesia or complete aneusthesia from damage to K nerves
- Etiology:
  - Decreased tear film
  - Damaged epi BM
  - Toxicity from topical antivirals(?)
- Signs:
  - Starts as PEEs → Persistant epi defect
  - Defect is oval with smooth borders
NEUTROPHIC HSK
HSK TREATMENT
ARMAMENTARIUM -- TOPICALS

- Trifluridine 1% solution (Viroptic)
  - FDA approved in 1980; only topical antiviral during HEDS
  - Toxic to epi

- Ganciclovir 0.15% gel (Zirgan)
  - FDA approved in 2009
  - Dosed less and less toxic than trifluridine

- Acyclovir 3% ointment (Zovirax)
  - Not FDA approved but tolerated well world-wide
POLL QUESTION #4

The 1988 Nobel prize in Medicine was awarded to the scientists whose research led to the discovery of.....?

1. Azathioprine
2. Acyclovir
3. Allopurinol
4. Trimethoprim
ARMAMENTARIUM -- ORALS

• Acyclovir: Only antiviral available in HEDS
  – Poorly absorbed in GI tract; Bioavailability is 10-20%
  – Don’t need to renal dose unless <10 mL/min

• Valacyclovir: FDA approved in 1995 AND
  Famciclovir: FDA approved in 2006
  – Bioavailability around 50%; need to renal dose
  – Dosed 1-2x/day (vs 3-5x/day with acyclovir)
PREVENTION

• LASIK/PRK
  – There has been reports of reactivation of HSK following excimer laser
  – Recommendations to “give perioperative and postoperative antiviral therapy to all refractive surgery patients with a history of HSK infection”

• Corneal Crosslinking for Keratoconus
  – Similar reports of reactivation
  – Perhaps more so 2^ exposure to UV light
  – “Prophylactic antiviral therapy may decrease the possibility of herpetic keratitis after CXL in patients with a history of HSK.”

• Prostaglandin Therapy
  – More controversial
  – Anecdotal reports, but no large study correlation
  – Some providers consider not Rx-ing if h/o HSK
SUMMARY

• Make a Timely Diagnosis
• Think about Vaccines
• Think about new treatments
QUESTIONS/COMMENT/THOUGHTS/IDEAS?