

THE NEUROTROPHIC CORNEA

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DISCLOSURES

- Ocular Therapeutics
- Glaukos
- Horizon
- Quidel
- Eyevance
- Alcon
- Tarsus
- Thea
- Kala
- Inovis
- Orasis
- RVL
- Oyster Point
- Dompe

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WHY IS THE CORNEA IMPORTANT?

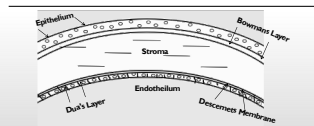
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CORNEAL FUNCTION

- Shields the eye from germs, dust, other harmful matter
- Contributes between 65-75% refracting power to the eye
- Filters out some of the most harmful UV wavelengths

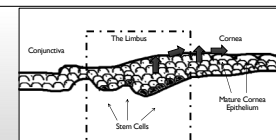
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CORNEAL ANATOMY



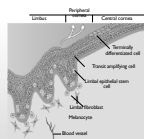
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LIMBUS



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CORNEAL EPITHELIAL CELLS



- Corneal integrity and function depends on a constant replenishment of epithelial cells
- Stem cells located in the limbus divide asymmetrically to produce:
 - Mature stromal cells
 - Cells that differentiate into epithelial cells as they migrate out of the limbus
- In the healthy cornea, production of new epithelial cells is sufficient to replace cells lost at the epithelial surface

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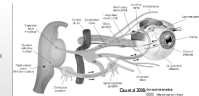
CORNEAL EPITHELIAL CELLS

- Corneal epithelial cells and keratocytes regulate the survival, differentiation and maturation of nerve fibres by releasing neurotrophins and growth factors, such as:
 - NGF
 - NT-3
 - NT-4
 - BDNF
 - BDNF
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 - BDNF
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 - BDNF

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CORNEA: RICHEST INNERVATION OF ALL BODY TISSUES¹

- Healthy cornea contains no blood vessels and is avascular in nature to pain
- Corneal sensory nerves originate from the ophthalmic branch of the fifth cranial nerve²
- Trigeminal nerve bundles have thick perineurium and myelin sheaths where they enter the corneal stroma at the corneal nerve limbus, thus increasing transparency of the cornea^{1,3}
- The cornea also receives some sympathetic innervation from the superior cervical ganglion²



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- Ocular Hx:
 - Dry eye syndrome – 10+ yrs
 - Herpes zoster keratitis OS
 - Anterior uveitis OS
 - PCMG - Mild OU
 - Pharyngitis OU
 - Phaco OU
 - Previous treatments:
 - Amniotic membrane OS (2019, 2020)
 - Punctal cautery (2011) OU
- Med Hx:
 - NIDDM 15 yrs
 - Osteoarthritis
 - Hypothyroid
 - Seasonal allergies
 - Med:
 - Cimetidine
 - Lactulose
 - Tirofene

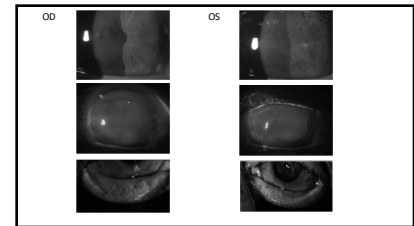
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CLINICAL EXAM

- Lids / Lashes – Clear and good position
- Conjunctiva – or injection OU
- Cornea:
 - CD 3+ Inf SPK
 - OS Dense SPK, 1+ K edema
- A/C – Deep and Quiet
- PCIOU OU
- IOP – 11 mmHg OU

Anything else we should add???

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DIFFERENTIALS??

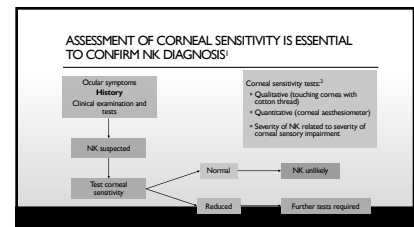
WHAT ABOUT K SENSITIVITY TESTING?

TREATMENTS??

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CORNEAL SENSITIVITY TESTING

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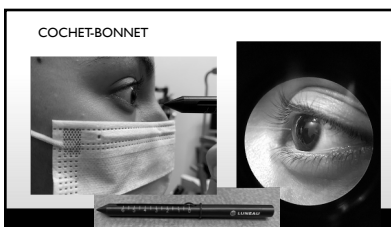


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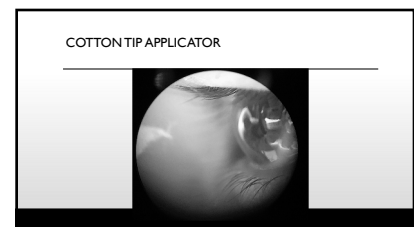
CORNEAL SENSITIVITY TESTING: ESTHESIOLOGY

- Qualitative
 - Cotton tip applicator
 - Dental floss
- Quantitative
 - Cochet-Bonnet

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CASE #2

- 57 YOA caucasian male
- CC: Progressive decrease in vision over the last 1 month with sharp change in the last week.
- OHL: CL overwear (when prompted says he has had to peel them off his eyes the last few months)
- No systemic Hx or medications

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- BCVA OD: 20/400 OS: HM 5ft
- IOP App 16mmHg OD and OS
- SLE
 - OS=OD: 3+ stippling in whorl like pattern, moderate haze with central line (conjunctivalization)

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IS IT LSCD OR NK.....OR BOTH!

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TREATMENT

- Topical corticosteroid BID OU
- Cyclosporine BID OU
- Hylo-Vic A ointment at night
- PFAT every 2 hours or more
- Next appointment No Touch

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TREATMENT OF NK

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STAGE I

- Remove any ocular medication that may be associated with toxicity
 - Preservative free options, tears and ointments
- Treat other associated ocular problems
 - LSCD
 - OSD/DED
 - Exposure keratitis

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STAGE 2

- Promotes healing of epithelial defect and prevent corneal ulcer
- Monitor patient frequently
- Topical antibiotics
 - Steroids sparingly
- Bandage contact lens
- Vitamin A ointment
- Amniotic membranes
- Autologous serum eye drops
 - Growth factors, neurotrophins, cytokines, vitamins

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AMNIOTIC MEMBRANE FOR NK

- Khokhar et al 2005
- 30 patients given either amniotic membrane or tarsorrhaphy and bandage CL
- 3 months
 - 10/15 patients receiving tarsorrhaphy or bandage CL had full epithelialization and healing
 - 11/15 patients receiving amniotic membrane tx had full epithelialization and healing

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AUTOLOGOUS SERUM TEARS FOR NK

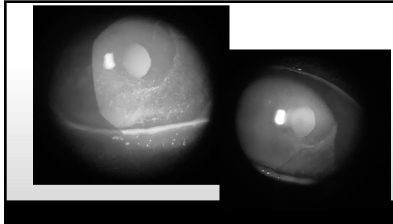
- Matsumoto et al 2004
- Complete healing of all the 14 eyes with NK treated with autologous serum drops and an increase in corneal sensitivity in 64.2% of cases
- The study demonstrated that serum harbors neurotrophins and growth factors to the ocular surface.
- More recent studies confirmed that autologous serum eye drops allowed high rates of corneal healing, and also the improvement of corneal nerve morphology with increased number, length, width, and density

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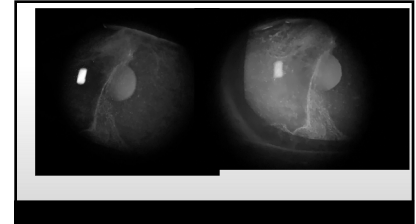
SURGICAL INTERVENTION

- Tarsorrhaphy
- LSC transplant
- Cyanoacrylate glue for small perforations
- Penetrating keratoplasty
- Lamellar keratoplasty

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FOLLOW UP

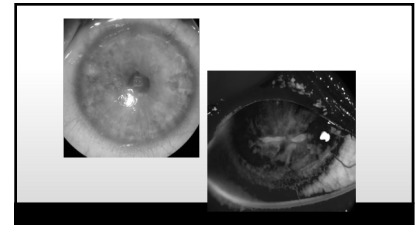
- Vision improved
 - BCVA OD 20/70, OS 20/400
- Corneal devascularization declined
 - 100% desensitized OU
- DryAMG OS
 - Continue all other therapies except Hydroxy-A-QS discontinue, start MaxRhoase BID OS
 - Returned but with significant improvement in signs and symptoms
 - BCVA OD 20/30, OS 20/180
 - Dry AMG placed OS again

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CASE #2.5

- 17 YOA White Female
- Painful, persistent epithelial Defects OU x 2 months
- 100% Desensitized corneas OU
- Autoimmune polyendocrinopathy

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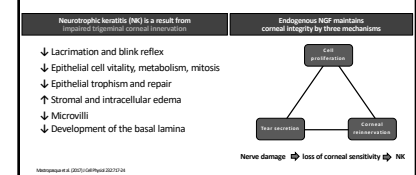
DX STAGE 2 NK

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NEW TREATMENT WITH NGF

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Endogenous nerve growth factor (NGF) and its role in NK:



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PATIENT #3 ROCK SALT TO THE EYE

- 40 YOA White Female
- Got rock salt in her OS 2 years previously in NYC when walking around outside her hotel.
- Pain and light sensitivity still present and persistent.
 - No improvement with aggressive dry eye treatment
 - Only improvement is with sun glasses and photochromatic CL

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WHAT'S REALLY GOING ON HERE?

- Corneal sensitivity
 - 100% sensitivity OD, 50% sensitivity OS
- Started on topical congenerim Q2hr x 8 weeks
 - Improvement to approximately 70% sensitivity OS

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NEUROPATHIC CORNEAL PAIN

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- Persistent ocular pain
 - Burning
 - Increased light sensitivity
 - Increased sensitivity to wind
 - Shooting pains from one or both eyes
- May be present WITH or WITHOUT ocular surface abnormalities

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WHAT CAUSES THIS?

- Suggested that there is an initial insult to the eye causing chronic nerve abnormality
- The initial trigger may be any of the following:
 - trauma (e.g., corneal abrasion, radiation therapy)
 - chemical exposures (e.g., preservatives in topical medications, chemical burns, systemic chemotherapy)
 - infection (e.g., herpes simplex virus, herpes zoster virus)
 - eye surgery (e.g., refractive, cataract, glaucoma, and retinal surgery)
 - systemic disease (e.g., autoimmune or inflammatory conditions, diabetes, fibromyalgia)
 - other neurological disease (e.g., trigeminal neuralgia, migraine)

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Topical Recombinant Human Nerve Growth Factor Improves Outcomes in Murine Model of Neuropathic Corneal Pain

Yanling Zhang, Stephen J. Hwang, Yanling Qiu, David Chen, Nathan Spedding, Prabhu Narasimhan

Author Affiliations & Notes

Investigator Confirmed by Visual Neuroscience 2021: 16103, 162, 163

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STUDY METHOD

- Adult Male mice underwent ciliary nerve ligation to induce NCP
- Treated with 6 10uL drops/day of 0.02mg/mL rhNGF or vehicle
- Outcomes @ day 7,10,14:
 - corneal fluorescein stain
 - Cochet-Bonnet esthesiometry
 - Littered for assessment of pain by jaw wipe response
- Day 14 trigeminal ganglia were removed and analyzed for neurotrophic factors and cytokines

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RESULTS

- Did not alter the corneal fluorescein staining or the corneal sensitivity in either group
- Reduction in several neurotrophic factors in the treatment group vs the vehicle only
 - No increase in pro-inflammatory cytokines
- Findings suggest that topical rhNGF treatment improves pain outcomes in our neuropathic corneal pain and warrant future studies in the clinic
- Topical rhNGF treatment alters expression of neurotrophic factors, but not pro-inflammatory cytokines within the TG

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PATIENT #4 PAIN WITHOUT STAIN

- 47 YOA African American Female
- Referred by Optometrist for corneal evaluation. Ongoing and constant foreign body sensation, discharge worsening. Recently began to have light sensitivity and sensation that her eye was on fire
 - Thill, given with antibiotic, and steroid
 - Removed yesterday and continues to have no improvement
 - OS-OD

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FINDINGS

- BCVA OD 20/20; OS 20/30
- Lids: clear OU
- Cornea: white and quiet with no follicles or papillae OU
- Cornea: OD 4 second TBUT; OS 5PK; ABMD: OS ABMD 1+SPK
- AC: deep, dark and quiet OU
- Lens: 0+ NS OU
- Corneal sensitivities: OD: 1st 2 quadrants 100% desensitized; 50% Sup/Inf; OS: all 4 quadrants 100% desensitization

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TREATMENT #1

- PF Dexamethasone QID OU
- PF Tears PRN
- Prokers placed in office OS

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RETURN

- Improved Sensitivity OU by approximately 50-75%, improvement in symptoms OS
- Corneal findings: OU ABMD 1+ SPK
- Continue Topical treatment, hold on Prokers OS

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2 WEEKS LATER

- Patient came in early 2/2 worsening of symptoms OS
- OU ABMD, 9 second TBUT, 1+ SPK OU
- Time to elevate treatment...
 - Cenergem Q2hr x 8 weeks

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4 WEEKS INTO TREATMENT

- Cornea: No staining, 10 second TBUT OU
- Improvement in symptoms of light sensitivity and pain
- Corneal Sensitivity: OD>OS 25% desensitization

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2 WEEKS AFTER TREATMENT

- Patient was able to drive to appointment without sun glasses
- Corneal Sensitivity: 10% or less desensitization OU
- Re-treat?

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FUTURE TREATMENTS

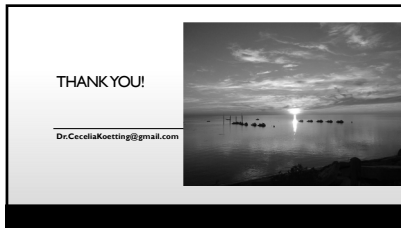
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Study	Sex (n)	Treatment	Protocol	Observation period (days)	Complete healing	Healing time (days)
Adler et al. ¹⁸	11	BCVA	1st observation day	115	72.7%	40.9
Araki et al. ¹⁹	8	BCVA	1st observation day	45	100%	36
Chen et al. ²⁰	9	Thymosin beta 4	4-day	142	67%	45
Hidve et al. ²¹	9	GF and GF1	4-day	141	89%	13.3
Shimada et al. ²²	26	GF and GF1	4-day	96	73%	16.5
Uchikawa et al. ²³	14	HAZ	Day 1 for 3 days, Post-healing	45	100%	21
Brown et al. ²⁴	45	HAZ	Day 1 for 3 days, Post-healing	38	100%	22.8/26.4
Lee et al. ²⁵	27	Atropine (0.01%)	11 mg 1-day	140	85%	15.4

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QUESTIONS?

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