

It's All In Their Head: Diagnosing Neurological Related Eye Conditions



CECELIA KOETTING OD FAAO DIPABO
UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

1

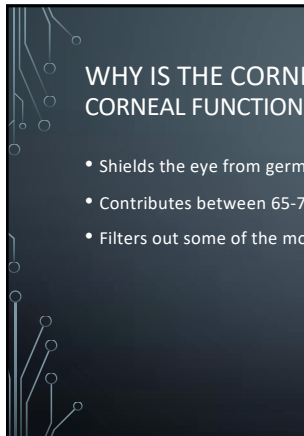
Cecelia Koetting Financial Disclosures

"All relevant relationships have been mitigated."

• Horizon-C	• Glaukos-C	• Oyster Point/Viatris-C,R
• Ivantis-C	• B +L- C, S, R	• Allergan/Abbvie -C, S, R
• Orasis-C, S, R	• Iveric Bio-C	• Alcon-C, S, R
• Trukera (B+L) -C	• Azura-C	• Harrow-C, S
• LENZ-C	• Aldeyra-C	• Thea-C,R
• PRN-C,S	• Dompe-C,S,R	• Bruder-C
• Kala-R	• Myze- C	• Blinkjoy-C
• Tarsus-C,S,R	• MOVU- C	• SCOPE-C
• Topcon-C	• Vital Tears- C	• Brill- C

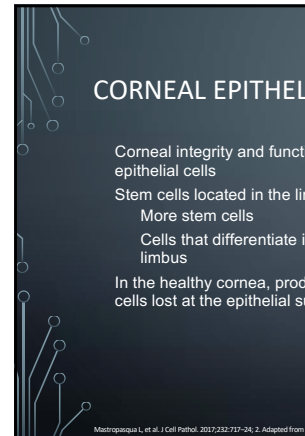
3



WHY IS THE CORNEA IMPORTANT? 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

4



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:

- More stem 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

Mastropasqua L, et al. J Cell Pathol. 2017;232:717-26, 2. Adapted from Shaheen R, et al. Surv Ophthalmol. 2014;59:263-85.

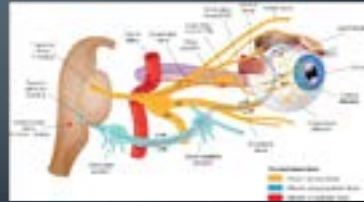
5

HIGHEST CONCENTRATION OF NERVES

Healthy cornea contains no blood vessels and is extremely sensitive to pain¹

Corneal sensory nerves originate from the ophthalmic branch of the trigeminal nerve

Cornea also receives sympathetic innervation from the superior cervical ganglion



1. Mastroianni L, et al. J Cell Pathol. 2017;232:717-24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:525-42; 3. Tsou HS, et al. Prog Retin Eye Res. 2008;28:30-59; 4. Muroyama T, et al. J Cell Pathol. 2017;232:717-24.

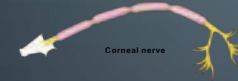
6

NERVES, NERVES, NERVES

Neuromediators¹

Substance P
Neurokinin A
Calcitonin gene-related peptide
Acetylcholine
Cholecystokinin
Galanin
Noradrenaline

Serotonin
Neuropeptide Y
Vasointestinal peptide
Met-enkephalin
Brain natriuretic peptide
Vasopressin
Neurotensin
Beta endorphin



Job #1: react to injury at the ocular surface by registering pain and irritation and triggering **protective reflexes**, such as **tear production and blinking**¹

Job #2: release neuromediators that provide **trophic support** to corneal epithelial cells and keratocytes^{1,2}

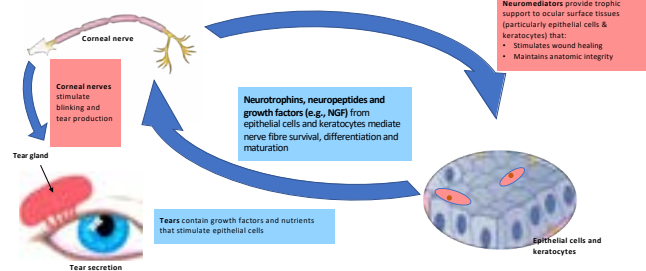
Images by kind permission of Prof. G. G. G.

1. Mastroianni L, et al. J Cell Pathol. 2017;232:717-24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:525-42.

7

Corneal homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis



Adapted from Mastroianni L, et al. J Cell Pathol. 2017;232:717-24.

8

NEUROTROPHIC KERATITIS

- Rare disease
 - Fewer than 65,000 in the US****
- Degenerative corneal disease caused by damage of the trigeminal corneal innervation
 - Breakdown of epithelium
 - Corneal ulceration

Sheth M, Lambiase A, et al. Cornea. 2014;33:1000-1005; 2. Lambiase A, et al. Cornea. 2014;33:1000-1005; 3. Lambiase A, et al. Cornea. 2014;33:1000-1005; 4. Lambiase A, et al. Cornea. 2014;33:1000-1005.

9

CASE #1

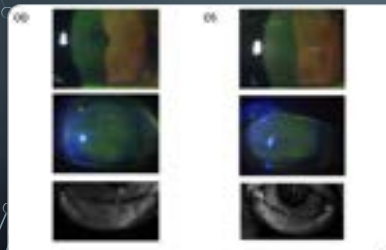
- The 84 year old, AA female presents for 3-4 month DES check (no touch) and MMP-9 testing.
- Pt has a h/o DES and POAG mild OU.
- Pt states OS>OD has some itching.
- She has only been using her cyclosporine 0.05% and AT's. She never picked up fluoromethalone drops and is not using AT's ointment or a heat mask.

16

- Ocular Hx:
 - Dry eye syndrome – 10+ yrs
 - Herpes stromal keratitis OS
 - Inactive – Last episode 2020
 - Anterior scleritis OS
 - Inactive
 - POAG - Mild OU
 - Pterygium sx OU
 - Phaco OU
 - Previous treatments
 - Amniotic membrane OS (2019, 2020)
 - Punctal cautery (2011) OU
- Med Hx:
 - NIDDM 15 yrs
 - Osteoarthritis
 - Hypothyroid
 - Seasonal allergies
- Meds:
 - Ceterizine
 - Lactulose
 - Tirosint

17

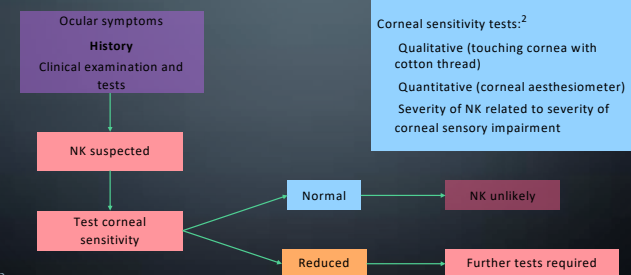
CLINICAL EXAM



- Lids / Lashes – Clear and good position
- Conjunctiva – tr injection OU
- Cornea
 - OD 1+ Inf SPK
 - OS 1-2+ fine diffuse SPK, 1+ K edema
- A/C – Deep and Quiet
- PCIOU OU
- IOP – 11 mmHg OU

18

ASSESSMENT OF CORNEAL SENSITIVITY IS ESSENTIAL TO CONFIRM NK DIAGNOSIS¹



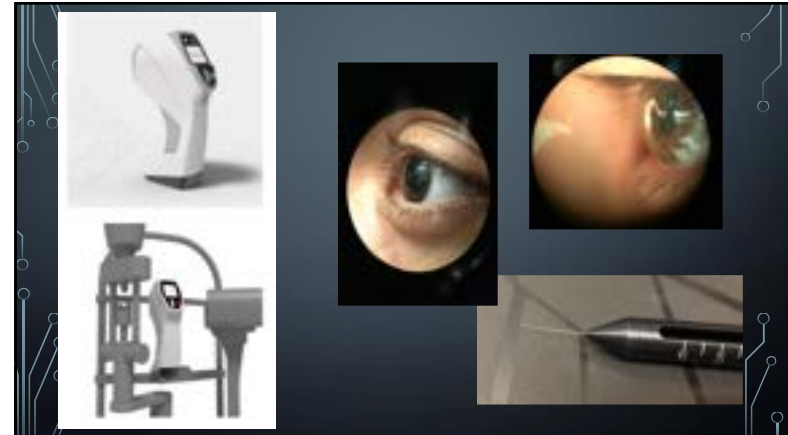
19

CORNEAL SENSIVITY TESTING: ESTHESIOMETRY

- Qualitative
 - Cotton tip applicator
 - Dental floss
 - Tissue paper
- Quantitative
 - Cochet-Bonnet
 - Belmonte Non contact gas esthesiometer
 - Brill esthesiometer



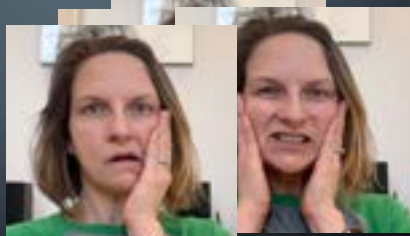
20



21

But wait. . .don't forget the other nerves!

- CN1 – Olfactory nerve
- CN2 – Optic nerve
- CN3 – Oculomotor nerve
- CN4 – Trochlear
- CN5 – Trigeminal
- CN6 – Abducens
- CN7 – Facial nerve
- CN8 – Acoustic nerve
- CN9 – Glossopharyngeal nerve
- CN10 – Vagus nerve
- CN11 – Accessory nerve
- CN12 – Hypoglossal nerve



23

But wait. . .don't

- CN1 – Olfactory nerve
- CN2 – Optic nerve
- CN3 – Oculomotor nerve
- CN4 – Trochlear
- CN5 – Trigeminal
- CN6 – Abducens
- CN7 – Facial nerve
- CN8 – Acoustic nerve
- CN9 – Glossopharyngeal nerve
- CN10 – Vagus nerve
- CN11 – Accessory nerve
- CN12 – Hypoglossal nerve



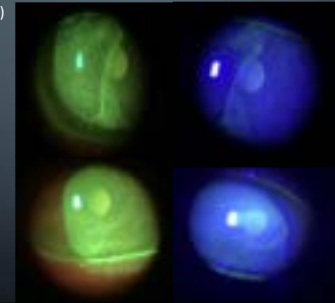
24

CASE #2

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

26

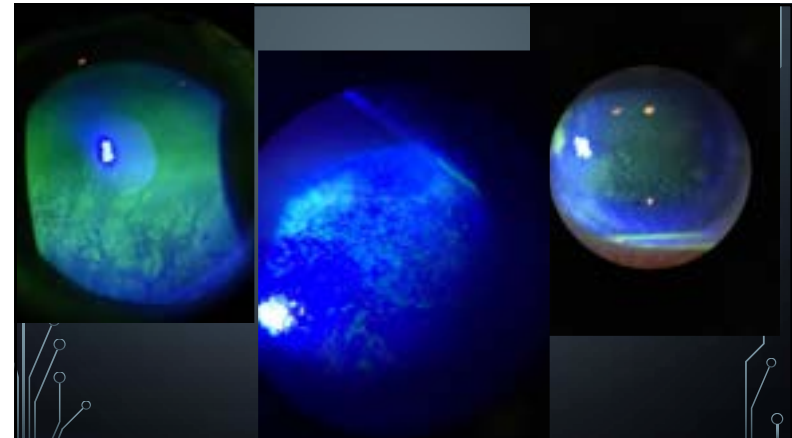
- BCVA OD: 20/400; OS: HM 5Ft
- IOP App 16mmHg OD and OS
- SLE:
 - OS>OD: 3+ stippling in whorl like pattern, moderate haze with central line (conjunctivalization)



27

SLIT LAMP EXAM WITH VITAL DYES ARE
IMPORTANT!

28



29

INITIAL TREATMENT FOR OUR PATIENT

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

30

STAGE 1

- 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
- Vitamin A ointment
- Amniotic membranes
- Autologous serum or PRP eye drops
 - Growth factors, neuromediators, cytokines, vitamins
 - Steroids
- Recombinant NGF Cenegermine

31

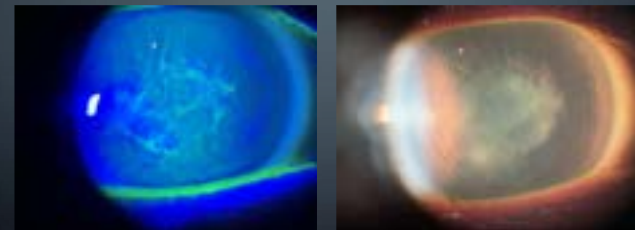
VITAMIN A OINTMENT

- Vitamin A regulates the proliferation and differentiation of corneal epithelial cells,
 - Preserves conjunctival goblet cells
- Vitamin A is an essential nutrient present naturally in tear film of healthy eyes
- Vitamin A plays an important role in production of the mucin layer



32

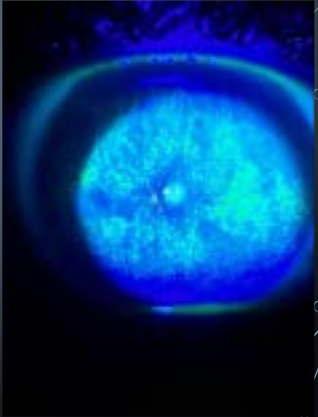
NK FROM RCE



33

STAGE 2

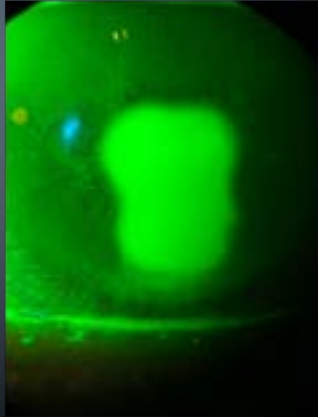
- Promote healing of epithelial defect and prevent corneal ulcer
- Monitor patient frequently
- Topical antibiotics
- Bandage contact lens



34

STAGE 3

- All the above
- Heavy antibiotics
 - Consider fortified
- Will need surgery if perforation



35

AMNIOTIC MEMBRANE FOR NK

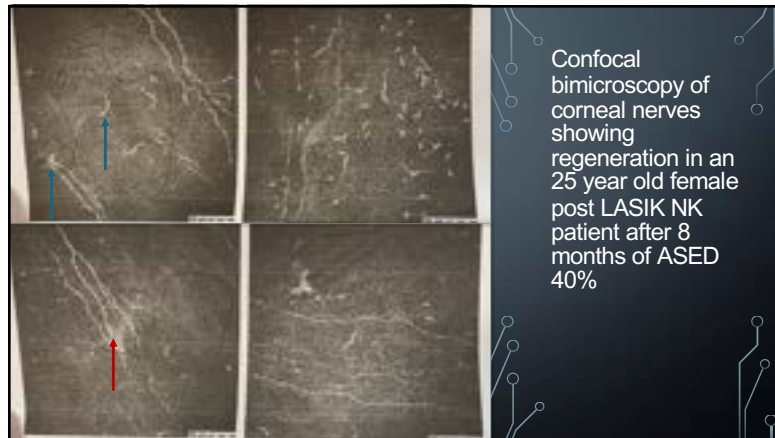
- Khokhar et al 2005
- 30 patients given either amniotic membrane or tarsorrhaphy and bandage CL
- 3 months
 - 10/15 patients receiving tarsorrhaphy or bandage CL had full epithelialization and healing
 - 11/15 patients receiving amniotic membrane tx had full epithelialization and healing

36

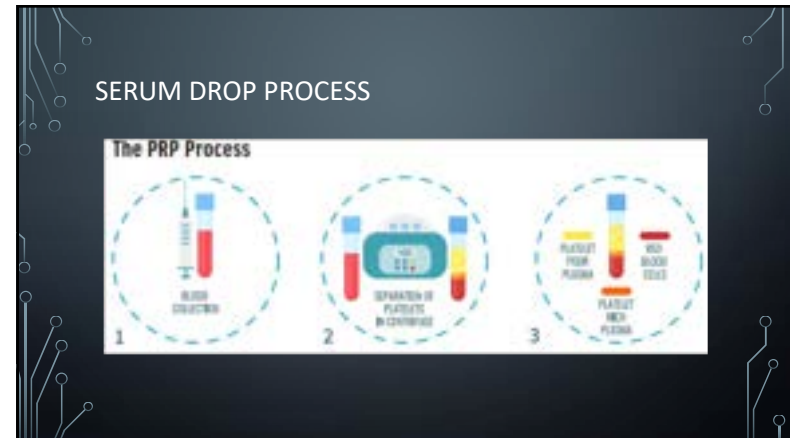
AUTOLOGOUS SERUM TEARS FOR NK

- 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

37



38



39

ASED VS PRP?

<h4>ASED</h4> <ul style="list-style-type: none"> • Does NOT contain platelets • Less concentration of GF/Plasma factors • Serum is not plasma • Has inflammatory cytokines • Contains high amounts of TGF-Beta – suppress wound healing • Diluted with saline (20-50%) to reduce inflammatory cytokines (further dilutes GF) 	<h4>PRP</h4> <p>Considered superior to autologous serum</p> <ul style="list-style-type: none"> • PRP contains Platelets • Contains higher concentration of growth factors • GF released in a biologically relevant ratio • Does not contain inflammatory cytokines • Not diluted with saline • Dispensed 100% • PRP is used in medicine and dentistry
--	--


40

SURGICAL INTERVENTION

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


41

CORNEAL NERVE SURGERY



Direct neurotization

utilizes the supraorbital and supratrochlear branches of the frontal nerve
sensory function of the two nerves overlap over the medial forehead, so harvesting one for a corneal neurotization surgery should theoretically leave adequate residual sensation



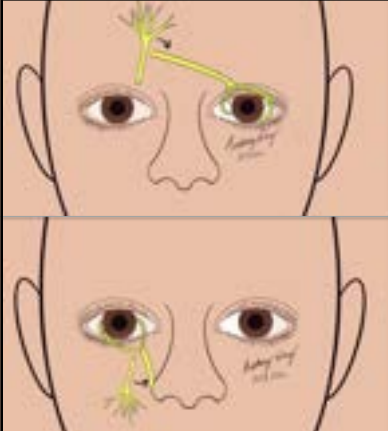
Indirect neurotization

utilizes sural nerve due to accessibility and low risk donor graft site in other neurotization procedures

- Provides sensation in calf region of leg and has branches from tibial and common fibular nerve
- great auricular nerve has been used in corneal neurotization surgeries and one advantage is its proximity to the recipient site as well as the need to only prepare one surgical field

42

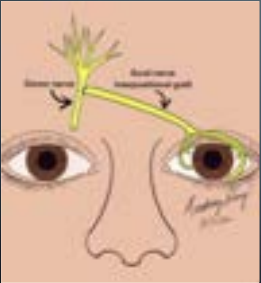
DIRECT NEUROTIZATION



- Ipsilateral grafts
- Contralateral Supraorbital/Supratrochlear Nerve Direct neurotization

43

INDIRECT NEUROTIZATION



- Sural nerve graft to ipsilateral or contralateral supraorbital/supratrochlear nerve Indirect Neurotization
- Greater Auricular Nerve Interpositional Graft to Contralateral Supratrochlear Nerve Indirect Neurotization
- Sural Nerve Interpositional Graft to Ipsilateral Greater Auricular Nerve Indirect Neurotization

44

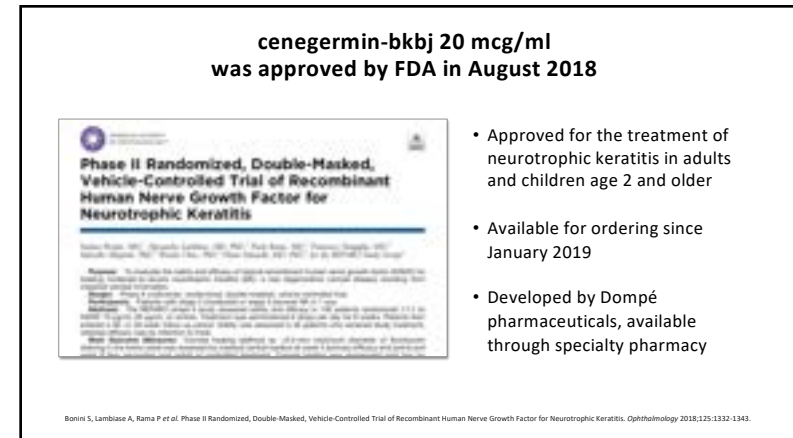
Follow Up on patient

- Vision improved
 - BCVA OD 20/70; OS 20/400
- Corneal desensitization checked
 - 100% desensitized OU
- Dry AMG OS
 - Continue all other therapies except Hylo Vit A OS discontinue, start Moxifloxacin BID OS
 - Over the next 6 months several AMG placed OS and a round of Cenegeimin
 - Final BCVA OD 20/20, OS 20/40
 - OS struggling with LSCD
- April 2024
 - Corneal specialist at UC decided time for Cattract surgery.
 - Seen 2 months post operative OU standard PCIOI.
 - Vision OD 20/20, OS 20/30
 - No active LSCD, scarring OS 11-2 o/c superior under lid
 - PATIENT ECSTACTIC! And me too ☺

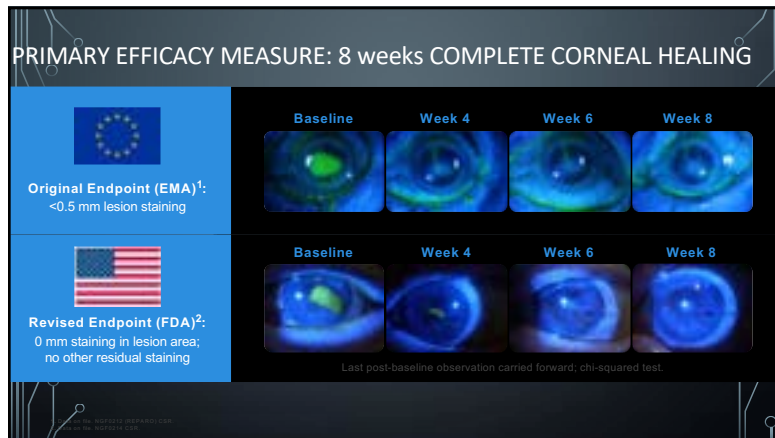
45



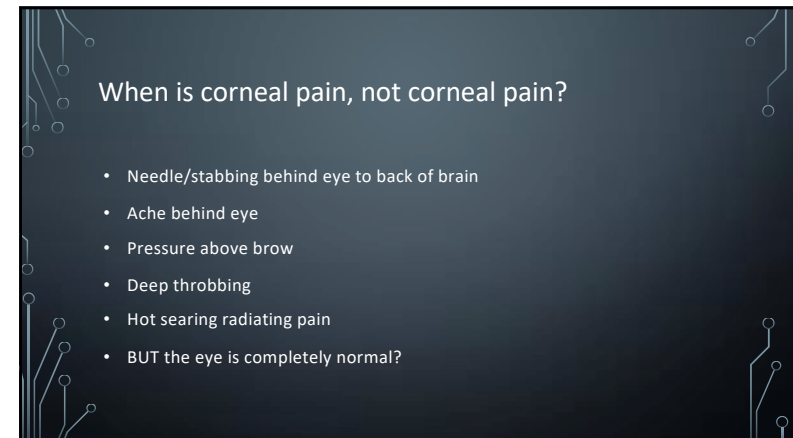
46



47



48



49

Conjunctivochalasis with Microblepharospasm

- Blinking with mechanical rubbing causes irritation and inflammation
- Oculoplastics?
 - Functional botox?
 - Surgical resection of conjunctiva

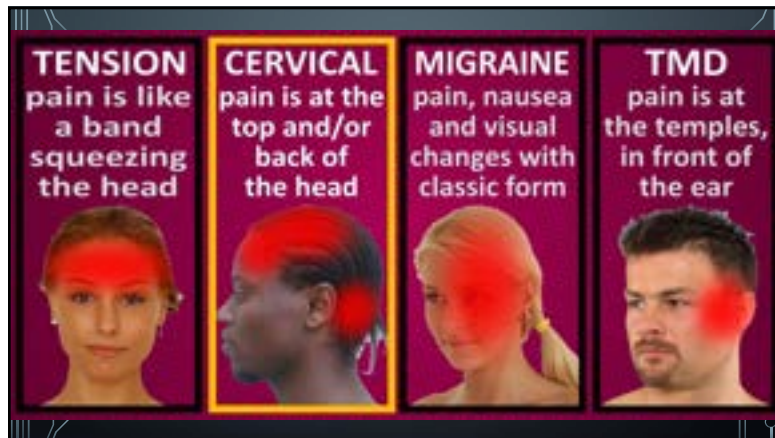


50

When eye is a pain in the neck

- Post TBI
 - Neck injury or whiplash common
- Post surgery
- Ergonomics of sitting and working on computer
- Do they have worsening of pain when reading, especially on a computer screen?
 - Saccadic eye movement
 - Neck muscles engage to keep head still while eyes move for saccades
 - If someone has a neck injury to these supporting muscles, when a patient uses a lot of saccades doing visual tasks can trigger pain
- Sensory nerves in the neck overlap with some trigeminal sensory nerves of the eye
 - Trigger points

51



52

Cervicogenic referred ocular pain and Cervicogenic Headache

- Referral to Orthopaedic Physical Therapist
- Headache clinic
- Possible treatments include:
 - Physical therapy
 - Massage therapy
 - Point trigger release
 - Botox
 - Acupuncture
 - Ergonomics



53

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

54

PROPARACAINE CHALLENGE

- Instill a drop of proparacaine
 - Does the patient still have pain?
 - Yes - then the issue is further back in the trigeminal nerve than the eye
 - No - then ocular pain is ocular surface related
 - Only works on nociceptors on they ocular surface.

55

WHATS REALLY GOING ON HERE?

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

56

Trigeminal Nerve Damage and NEUROPATHIC CORNEAL PAIN

- 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

57

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)

58

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

Wenbin Wang, Lianxin Chen, Hanyu Zhang, Shu Zhang, Liang Zhang, Xueqin Zhang, Xueqin Zhang, Xueqin Zhang

Journal of Neurology, Neurosurgery & Psychiatry

Investigative Ophthalmology & Visual Science June 2021; Vol 62, No 12

Abstract

Purpose: Since the discovery, nerve growth factor (NGF) has sparked widespread interest in possible therapeutic utility across neurologic diseases. NGF and other neurotrophic factors are upregulated in neuropathic pain, although their precise role remains to be fully understood. Herein, we assess the possible therapeutic benefit of recombinant human NGF (rhNGF) in the ciliary nerve ligation model of neuropathic corneal pain.

59

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
 - L-methtol for assessment of pain by paw wipe response
- Day 14 trigeminal ganglia were removed and analyzed for neurotrophic factors and cytokines

60

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

61

FUTURE TREATMENTS

Study	Eyes (no.)	Treatment	Posology	Onset-treatment interval (days)	Complete healing	Healing time (days)
Aifa et al ¹⁴	11	RGTA	1x/on alternate days	>15	72.7%	60.9
Arvola et al ¹⁵	6	RGTA	1x/on alternate days	45	33%	56
Dunn et al ¹⁶	9	Thymosin beta-4	4x/day	>42	67%	45
Nahida et al ¹⁷	9	SP and IGF1	4x/day	141	89%	13.3
Yamada et al ¹⁸	26	SP and IGF1	4x/day	96	73%	10.5
Lombase et al ¹⁹	14	NGF	Every 2 h for 2 days, then 6x/day	45	100%	21
Borini et al ²⁰	45	NGF	Every 2 h for 2 days, then 6x/day	38	100%	22.8/26.6
Lee et al ²¹	27	Nicergoline (oral)	10 mg 2x/day	>60	85%	15.6

62

FUTURE TREATMENTS

Topical Insulin Drops

Trefoil (TTHX1114) in studies for endothelial disease and neurotrophic keratitis

OK-101- Neuropathic pain-Phase 2 studies

63

PEARLS

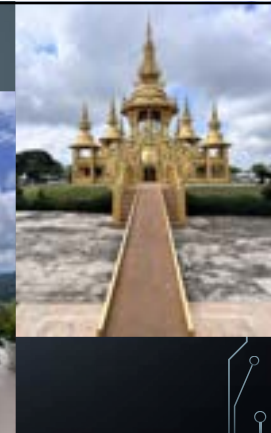
- When you've thrown the kitchen sink at a dry eye patient and its not better, check the corneal sensitivity
- Stain without pain, check corneal sensitivity
- Pain without stain, check NaFl with wratten filter or LG AND check corneal sensitivity
- NK is classified as a rare disease, but its more likely that its just under diagnosed

SO, Don't lose your nerve, CHECK CORNEAL SENSITIVITY!!

64

DR.CECELIAKOETTING@GMAIL.COM

THANK YOU!



65