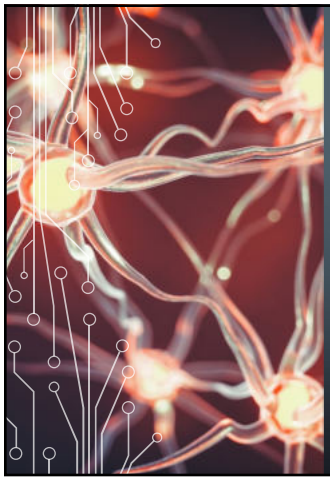


It's All In Their Head: Diagnosing Neurological Related Eye Conditions

CECELIA KOETTING OD FAAO DIPABO

UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

1

Cecelia Koetting Financial Disclosures

"All relevant relationships have been mitigated."

- Ocular Therapeutix
- Horizon
- Quidel
- Ivantis
- Orasis
- Trukera
- LENZ
- PRN
- Topcon

+ Glaukos
+ B +L
+ Iveric
+ Aldura
+ Claris Bio
+ Aldeyra
+ Twenty Twenty Therapeutics

- Oyster Point/Viatris
- Allergan
- Alcon
- Visus
- Thea
- Bruder
- Blinkjoy
- SCOPE

Intrepid

KOETTING

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

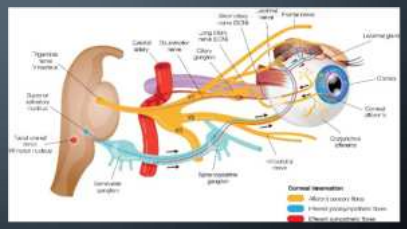
In the healthy cornea, production of new epithelial cells is sufficient to replace cells lost at the epithelial surface

Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Adapted from Shaheen B, et al. Surv Ophthalmol. 2014;59:263–85.

5

HIGHEST CONCENTRATION OF NERVES

- Healthy cornea contains no blood vessels and is extremely sensitive to pain[1]
- Corneal sensory nerves originate from the ophthalmic branch of the trigeminal nerve
- Cornea also receives sympathetic innervation from the superior cervical ganglion



1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42; 3. Jua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]

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NERVES, NERVES, NERVES

Neuromediators[1]

Substance P	Serotonin
Neurokinin A	Neuropeptide Y
Calcitonon gene-related peptide	Vasointestinal peptide
Acetylcholine	Met-enkephalin
Cholecystokinin	Brain natriuretic peptide
Galanin	Vasopressin
Noradrenaline	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. Dua

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

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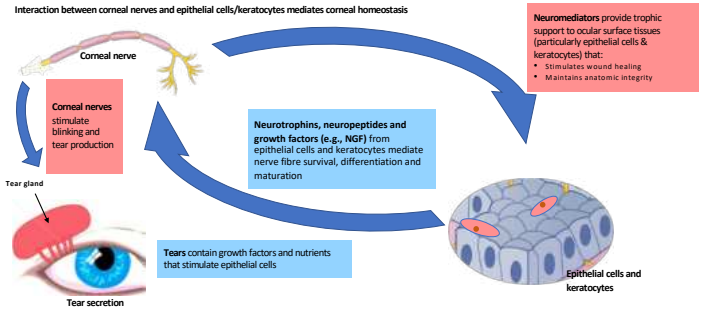
Corneal homeostasis



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

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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

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571–579.

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Corneal Nerve Damage is Central to NK

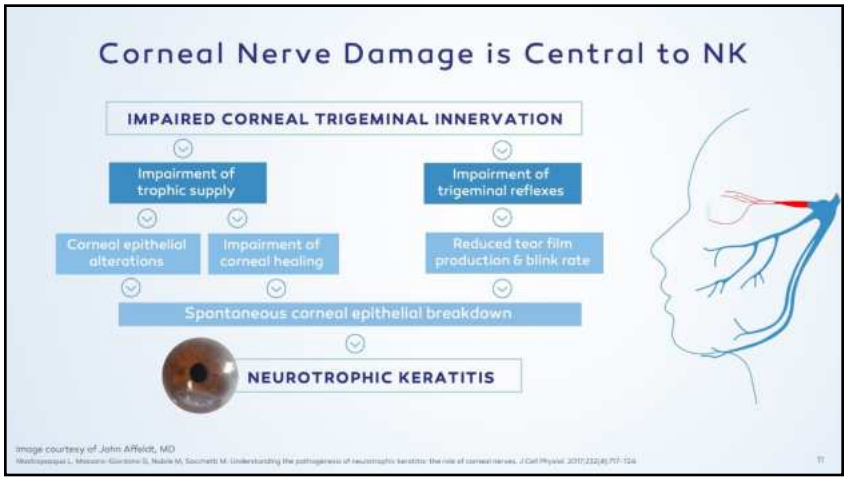

Image courtesy of John Affeldt, MD

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When was the last time you had a patient with neurotrophic keratitis?

1. In the last week
2. In the last month
3. In the last 6 months
4. I've probably had a patient with NK but maybe didn't know it at the time.

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ETIOLOGIES ASSOCIATED WITH NK

OCULAR
- Post-herpes infection
  - 6% of herpetic keratitis
  - 13% of herpes zoster keratitis
- Other infections with nerve damage
- Chemical and physical burns
- Abuse of topical anesthetics
- Drug toxicity
- Chronic ocular surface injury
- Contact lens wear
- Orbital neoplasia
- Corneal dystrophies

SYSTEMIC
- Diabetes
- Multiple sclerosis
- Vitamin A deficiency
- Leprosy
- Amyloidosis

GENETIC
- Riley-Day syndrome
- Goldenhar-Gorlin syndrome
- Moebius syndrome
- Familial corneal hypoesthesia

IATROGENIC
- Trauma to ciliary nerves by laser treatment and surgery
- Corneal incisions
- LASIK

CNS
- Neoplasm
- Aneurysms
- Stroke
- TBI/TBSI
- Degenerative disorders of the CNS
- Neurosurgical procedures
- Congenital/ developmental malformations (eg, trigeminal nerve hypoplasia)

CNS, central nervous system.

Dua HS, et al. *Prog Retin Eye Res*. 2018;66:107-131.

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MACKIE CLASSIFICATION

- Some vision loss can potentially be seen in all stages of NK[3]
- If untreated, moderate NK progresses to severe disease with associated risks of profound vision loss resulting from scarring and corneal perforation[3]

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NK Study Group (NKSD) Classification

Stage	NKSG	Mackie
Stage 1	Altered sensation without keratopathy	
Stage 2	Punctate epithelial keratopathy without stromal haze	Stage 1
Stage 3	Persistent/recurrent epithelial defects without stromal haze	Stage 2
Stage 4	PEK or PED WITH stromal haze	Stage ½
Stage 5	Persistent PED with corneal ulceration	Stage 3
Stage 6	Corneal perforation	Stage 3

Neurotrophic Keratopathy Study Group. *Ocul Surf.* 2023;30:129-138.

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A patient has an unhealing corneal abrasion with stromal haze but doesn't appear to have an active infection, what stage NK are they most likely?

1. Stage 2 Mackie
2. Stage 1 Mackie
3. Stage 3 NKSD
4. Stage 6 NKSD
5. Stage 2 Mackie or Stage 4 NKSD

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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.

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- 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

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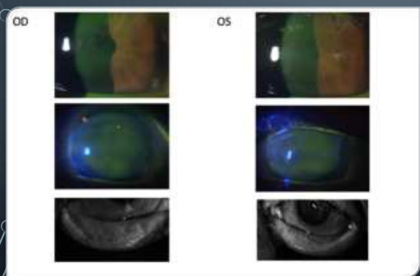
CLINICAL EXAM



- 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
- PCIOL OU
- IOP – 11 mmHg OU

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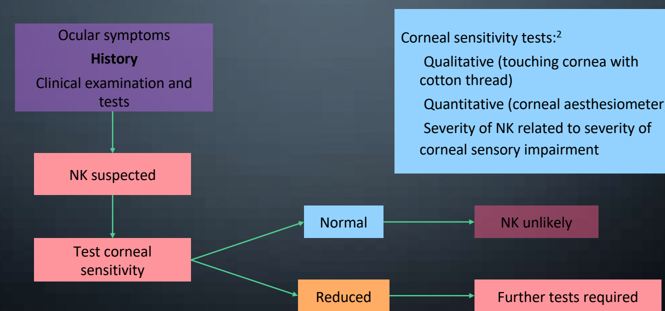
ASSESSMENT OF CORNEAL SENSITIVITY IS ESSENTIAL TO CONFIRM NK DIAGNOSIS[1]



Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

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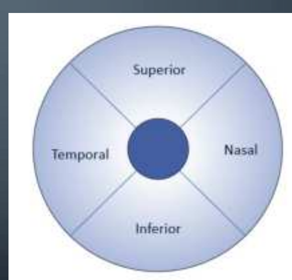
CORNEAL SENSITIVITY TESTING: ESTHESIOMETRY

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



20

21

Which nerves run through the cavernous sinus (pick all that apply)?

1. CN III
2. CN IV
3. CNV1
4. CNV2
5. CNVI

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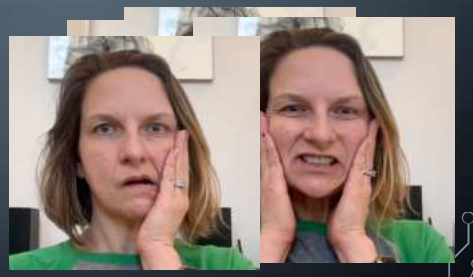
But wait. . .don't forget the other nerves!

- 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



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But wait. . .don't

- CN1 – Olfactory nerve
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- CN3 – Oculomotor nerve
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- CN6 – Abducens
- CN7 – Facial nerve
- CN8 – Acoustic nerve
- CN9 – Glossopharyngeal
- CN10 – Vagus nerve
- CN11 – Accessory nerve
- CN12 – Hypoglossal nerve

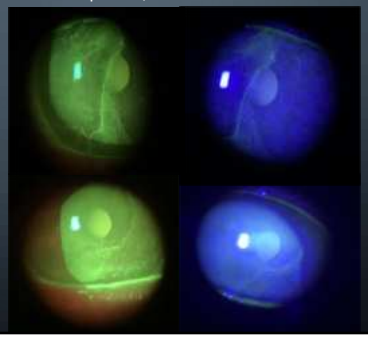
24

CASE #2

- 57 YOA causcasian 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)



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SLIT LAMP EXAM WITH VITAL DYES ARE IMPORTANT!

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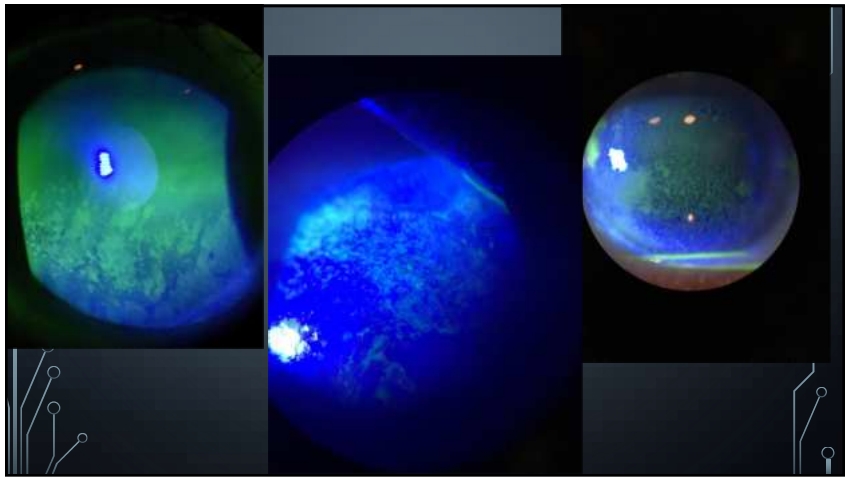

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INITIAL TREATMENT FOR OUR PATIENT

- Topical corticosteroid BID OU
- Cyclosporine BID OU
- Hylo Vit A ointment at night
- PF AT every 2 hours or more

- Next appointment No Touch

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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

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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

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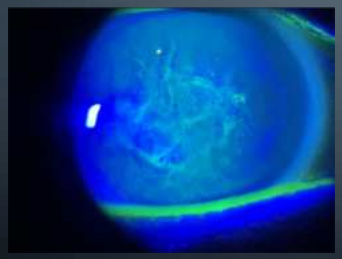
NK FROM RCE



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STAGE 2

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

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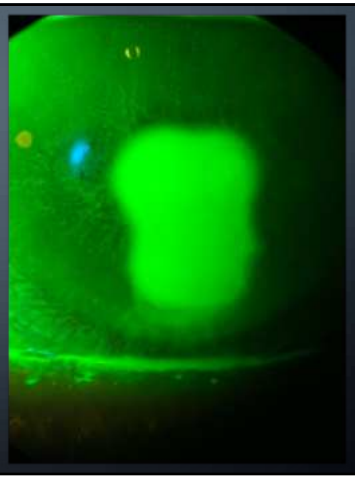
STAGE 3

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



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AMNIOTIC MEMBRANE FOR NK

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

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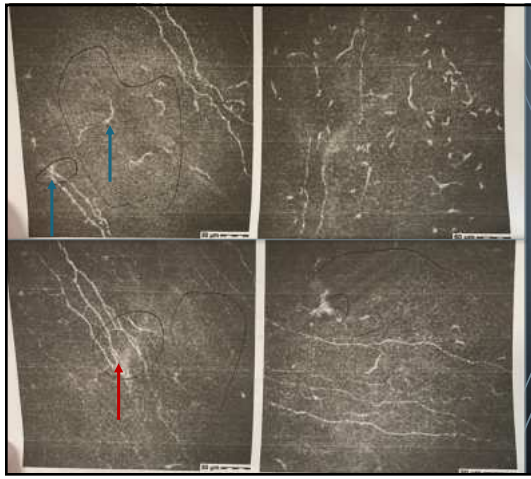

Confocal bimicroscopy of corneal nerves showing regeneration in an 25 year old female post LASIK NK patient after 8 months of ASED 40%

38

SERUM DROP PROCESS

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ASED VS PRP?

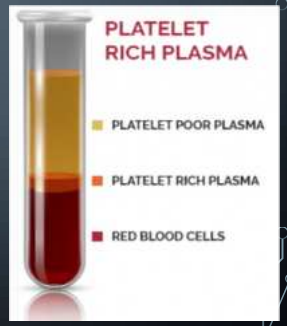
ASED

- 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)

PRP

Considered superior to autologous serum

- 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



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SURGICAL INTERVENTION

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

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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 fivular 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

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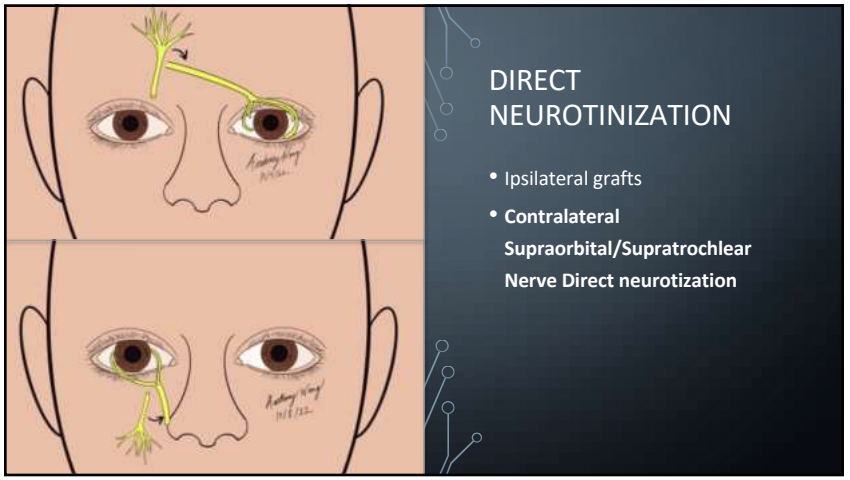

DIRECT NEUROTINIZATION

- Ipsilateral grafts
- **Contralateral Supraorbital/Supratrochlear Nerve Direct neurotization**

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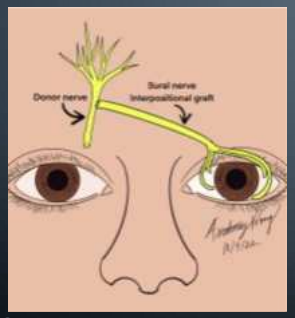
INDIRECT NEUROTIZATION



- **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**

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FOLLOW UP ON PT 2

- 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 Oxervate
  - Final BCVA OD 20/20//OS 20/40
  - OS struggling with LSCD

45

UPDATE ON THE LAST UPDATE

- 2 weeks ago
  - Hadn't seen in 3 months
  - No decompensation OU
  - Vision still OD 20/20; OS 20/40
  - LSCD in 4 clock hours OS, needs transplant but closest is California or Ohio
  - Discussed with cornea specialist other options. . .. Stay tuned

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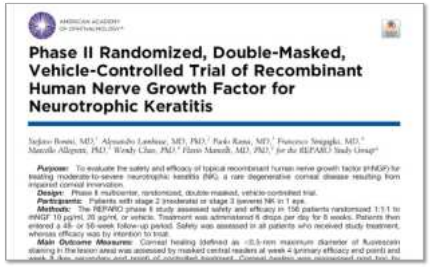
cenegermin-bkbj 20 mcg/ml
was approved by FDA in August 2018



Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.

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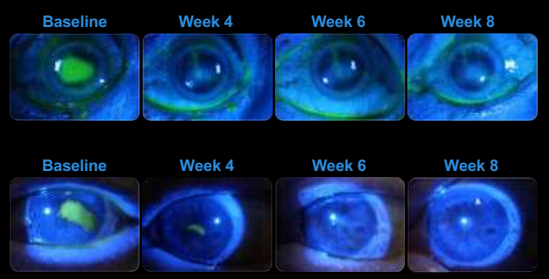
PRIMARY EFFICACY MEASURE: 8 weeks COMPLETE CORNEAL HEALING

Original Endpoint (EMA)[1]:
<0.5 mm lesion staining

Revised Endpoint (FDA)[2]:
0 mm staining in lesion area; no other residual staining



Last post-baseline observation carried forward; chi-squared test.

1. Data on file. NGF0212 (REPARO) CSR.
2. Data on file. NGF0214 CSR.

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When is corneal pain, not corneal pain?

- Needle/stabbing behind eye to back of brain
- Ache behind eye
- Pressure above brow
- Deep throbbing
- Hot searing radiating pain
- BUT the eye is completely normal?

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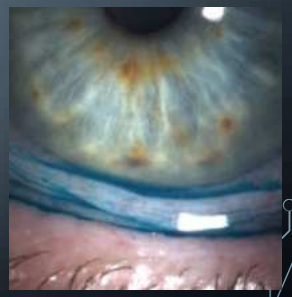
Conjunctivochalasis with Microblepharospasm

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



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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

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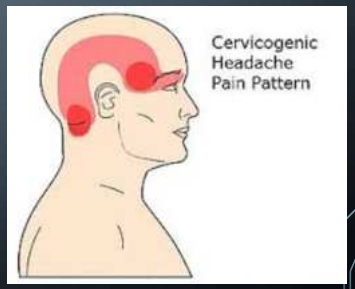
Cervicogenic referred ocular pain and Cervicogenic Headache

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



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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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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

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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

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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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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-metnthol for assessment of pain by paw 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-imflammatory 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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FUTURE TREATMENTS

Study	Eyes (no.)	Treatment	Posology	Onset-treatment interval (days)	Complete healing	Healing time (days)
Aifa et al[48]	11	RGTA	1x/on alternate days	>15	72.7%	60.9
Arvola et al[49]	6	RGTA	1x/on alternate days	45	33%	56
Dunn et al[50]	9	Thymosin beta-4	4x/day	>42	67%	45
Nishida et al[51]	9	SP and IGF1	4x/day	141	89%	13.3
Yamada et al[52]	26	SP and IGF1	4x/day	96	73%	10.5
Lambiase et al[53]	14	NGF	Every 2 h for 2 days, then 6x/day	45	100%	21
Bonini et al[3]	45	NGF	Every 2 h for 2 days, then 6x/day	38	100%	22.8/26.6[9]
Lee et al[54]	27	Nicergoline (oral)	10 mg 2x/day	>60	85%	15.6

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FUTURE TREATMENTS

Topical Insulin Drops

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

OK-101- Neuropathic pain-Phase 2 studies

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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!!

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THANK YOU!

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