



## IT'S ALL IN THEIR HEAD: DIAGNOSING NEUROLOGICAL RELATED EYE CONDITIONS

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## Cecelia Koetting Financial Disclosures

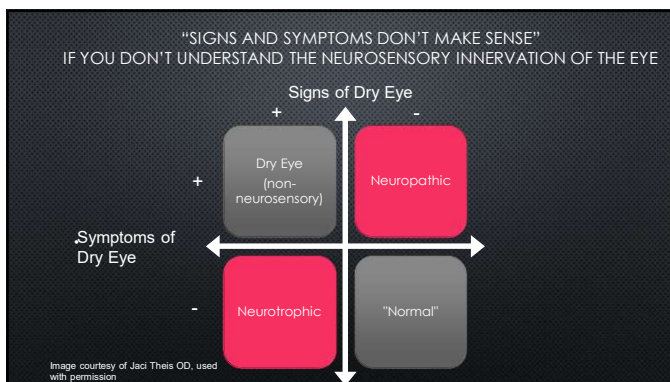
"All relevant relationships have been mitigated."

|                    |                  |                         |
|--------------------|------------------|-------------------------|
| • Orasis-C, S, R   | • Glaukos-C      | • Viatris-C,R           |
| • Trukera (B+L) -C | • B +L- C, S, R  | • Allergan/Abbvie -C, R |
| • PRN/EyePromise-C | • Azura-C        | • Alcon-C, S, R         |
| • Tarsus-C,S,R     | • Dome-C,S,R     | • Harrow-C, S           |
| • Topcon-C         | • Myze- C        | • Blinkjoy-C            |
| • Tenpoint-C       | • MOVU- C        | • Vicci- C              |
|                    | • Vital Tears- C |                         |
|                    | + SCOPE-C        |                         |

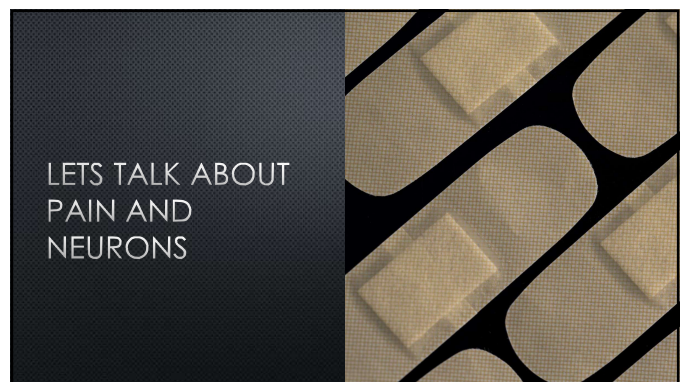
Intrepid



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## PAIN VS NOCIOCEPTION VS ITCH

- INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (IASP) 2020
  - PAIN= UNPLEASANT SENSORY AND EMOTIONAL EXPERIENCE ASSOCIATED WITH OR RESEMBLING THAT ASSOCIATED WITH, ACTUAL OR POTENTIAL TISSUE DAMAGE
  - NOCIOCEPTION= THE NEURAL PROCESS OF ENCODING AND PROCESSING NOXIOUS STIMULI
    - NOCIOCEPTION CAN HAPPEN WITH OR WITHOUT PAIN
  - SIMILAR TO DIFFERENCE BETWEEN SUBJECTIVE VS OBJECTIVE FINDINGS
- ITCH= UNPLEASANT SENSATION THAT LEADS TO SCRATCH OR DESIRE TO SCRATCH
  - CAN BE MECHANICAL OR CHEMICAL IRRITANTS
  - OR CAN BE DISEASED NEURONS
    - BURNING STINGING MAY COEXIST

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## NOCIOCEPTIVE PAIN TISSUE BASED

- CAUSE:** RESULTS FROM TISSUE DAMAGE AND INFLAMMATION LEADING TO ACTIVATION OF NOCIOCEPTORS
  - NON-NEURAL TISSUE // DETECTED BY NOCIOCEPTORS (PAIN RECEPTORS).
- CHARACTERISTICS:** USUALLY LOCALIZED, ACHING, THROBBING, ITCHING, OR SHARP. IT RESOLVES WHEN THE INJURY HEALS.
- EXAMPLES:** SPRAINED ANKLE, OSTEOARTHRITIS, SURGICAL INCISIONS, BROKEN BONES
  - INSULTS TO OCULAR SURFACE
    - INFECTION, TRAUMA, HIGH TEAR OSMOLARITY, INFLAMMATION
- VISCERAL VS SOMATIC

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### VISCERAL

PAIN ORIGINATING FROM VISCERA, MUSCLES, AND BONE IS DESCRIBED AS DULL AND DIFFUSE AND OFTEN POORLY LOCALIZED.

FREQUENTLY MEDIATED BY THE SLOWER, SMALL UNMYELINATED C-FIBERS.

PERCEIVED AS MORE UNPLEASANT THAN SOMATIC PAIN.

EXAMPLES FOR VISCERAL NOCICEPTIVE PAIN:

- TUMOR INVASION
- OBSTRUCTIONS (BOWEL, URETER, BILE DUCT)
- COLIC
- ANGINA
- PANCREATITIS

### SOMATIC

STIMULATION OF PERIPHERAL NOCICEPTORS CAPABLE OF RESPONDING TO STIMULI SUCH AS MECHANICAL (PRESSURE), THERMAL, CHEMICAL AND OTHER STIMULATION.

- COMMONLY DESCRIBED AS ITCHING OR SHARP, LOCALIZED PAIN THAT IS PREDOMINATELY BEING CARRIED BY FAST, MYELINATED A- $\alpha$ -FIBERS.
- EXAMPLES OF SOMATIC NOCICEPTIVE PAIN:
  - BURN
  - FRACTURES
  - INCISIONS, WOUNDS
  - CELLULITIS
  - SHINGLES
  - ARTHRITIS
  - GOUT
  - MUSCULOSKELETAL PAIN

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## NEUROPATHIC PAIN

### NERVE-BASED

- CAUSE:** A LESION OR DISEASE DIRECTLY AFFECTING THE SOMATOSENSORY NERVOUS SYSTEM, DAMAGE TO PERIPHERAL OR CENTRAL NERVES PERSISTING FOR >3 MONTHS
- CHARACTERISTICS:** BURNING, ELECTRICAL, SHOOTING, OR STABBING PAIN. OFTEN CHRONIC DUE TO POOR NERVE HEALING.
- EXAMPLES:** DIABETIC NEUROPATHY, POSTHERPETIC NEURALGIA (SHINGLES), PHANTOM LIMB PAIN, CARPAL TUNNEL SYNDROME.
- ETIOLOGY:**
  - DEGENERATIVE
  - TRAUMATIC
  - INFECTIOUS
  - METABOLIC
  - TOXIC



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## NOCIOPLASTIC PAIN

### SYSTEM-BASED/SENSITIZATION

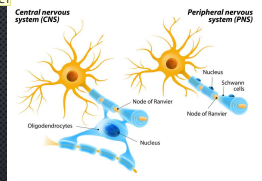
- CAUSE:** PAIN THAT ARISES FROM ALTERED NOCICEPTION DESPITE NO CLEAR EVIDENCE OF ACTUAL OR THREATENED TISSUE DAMAGE". IT INVOLVES CENTRAL SENSITIZATION, WHERE THE CENTRAL NERVOUS SYSTEM BECOMES OVERLY SENSITIVE.
- CHARACTERISTICS:** OFTEN WIDESPREAD, DIFFUSE, AND NOT EXPLAINED BY OTHER MECHANISMS. ASSOCIATED WITH FATIGUE, SLEEP DISTURBANCES, AND HYPERSENSITIVITY.
- EXAMPLES:**
  - FIBROMYALGIA, IRRITABLE BOWEL SYNDROME (IBS), NON-SPECIFIC CHRONIC LOW BACK PAIN, COMPLEX REGIONAL PAIN SYNDROME (CRPS).

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- NOCICEPTIVE:** "SOMETHING IS DAMAGING MY TISSUES."
- NEUROPATHIC:** "MY NERVES ARE DAMAGED."
- NOCIOPLASTIC:** "MY CENTRAL NERVOUS SYSTEM IS PROCESSING PAIN INCORRECTLY."
- AND OF COURSE THEY CAN BE MIXED

| Three Types of Pain! <sup>18</sup>                                                                                   |                                                                                                                  |                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| NOCICEPTIVE                                                                                                          | NEUROPATHIC                                                                                                      | NOCIOPLASTIC                                                                                    |
|                                  |                             |            |
| <b>Mechanism:</b> body's alarm system that activates when harmful stimuli trigger receptors to send signals to brain | <b>Mechanism:</b> lesion or disease in the nervous system caused by trauma, disease, chemicals or tumor invasion | <b>Mechanism:</b> changes in the nociceptive pathway without evidence of nerve or tissue damage |

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### CENTRAL PAIN

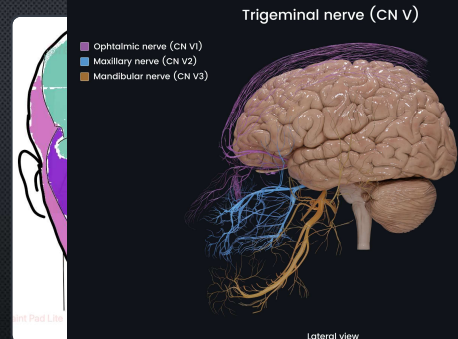
- ORIGIN:**
  - LESIONS OR DISEASES OF THE CENTRAL NERVOUS SYSTEM (CNS), THE BRAIN AND SPINAL CORD.
- CAUSES:**
  - STROKE, SPINAL CORD INJURY, MULTIPLE SCLEROSIS, PARKINSON'S DISEASE.
- CHARACTERISTICS:**
  - CAN INCLUDE PAIN FROM NON-PAINFUL STIMULI (ALLODYNIA), HEIGHTENED SENSITIVITY (LIGHS, SOUND), FATIGUE, COGNITIVE ISSUES, EMOTIONAL CHANGES (ANXIETY, DEPRESSION).
- MECHANISM:**
  - INVOLVES **CENTRAL SENSITIZATION**, WHERE PAIN PATHWAYS IN THE SPINAL CORD AND BRAIN BECOME HYPERSENSITIVE AND AMPLIFY SIGNALS.

### PERIPHERAL PAIN

- ORIGIN:**
  - LESIONS OR DISEASES OF THE PERIPHERAL NERVOUS SYSTEM (PNS), THE NERVES CONNECTING THE CNS TO THE BODY.
- CAUSES:**
  - TRAUMA, INFECTIONS (SHINGLES), METABOLIC ISSUES (DIABETES), TOXINS, COMPRESSION (CARPAL TUNNEL).
- CHARACTERISTICS:**
  - OFTEN BURNING, SHOOTING, STABBING PAIN, NUMBNESS, WEAKNESS, TYPICALLY IN HANDS/FEET.
- MECHANISM:**
  - INVOLVES PERIPHERAL SENSITIZATION, MAKING PERIPHERAL NERVE ENDINGS OVERLY SENSITIVE.

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### Trigeminal nerve (CN V)



Legend:

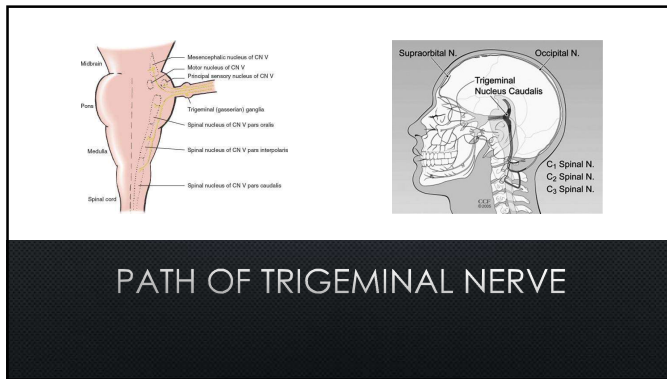
- Ophthalmic nerve (CN V1)
- Maxillary nerve (CN V2)
- Mandibular nerve (CN V3)

Source: Anatomy app

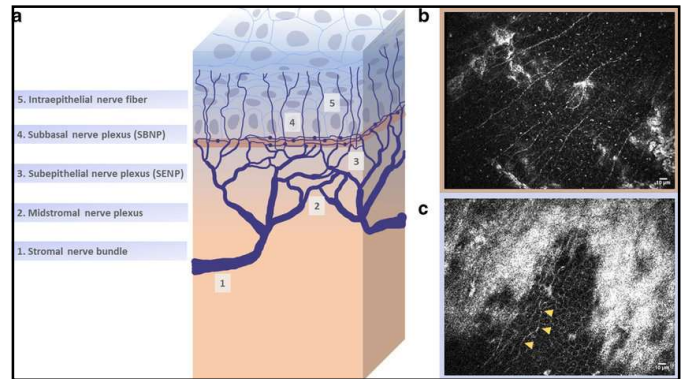
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### CORNEAL NERVES

- MAJORITY OF CORNEAL NERVE FIBERS ARE NOCICEPTIVE AND COLD THERMORECEPTOR FIBERS
- REMAINING FIBERS ARE SYMPATHETIC OR PARASYMPATHETIC POST-GANGLION FIBERS OF THE AUTONOMIC NERVOUS SYSTEM.
- C FIBERS**- THIN UNMYELINATED SLOW
  - POLYMODAL, RESPONSIVE TO NOXIOUS MECHANICAL, THERMAL, AND CHEMICAL STIMULI
- A-Δ FIBER**-FASTER CONDUCTING, POORLY MYELINATED TO MAINTAIN CORNEAL TRANSPARENCY
  - RESPOND TO NOXIOUS MECHANICAL AND THERMAL STIMULI
- AUTONOMIC NERVOUS FIBERS OF SYMPATHETIC (UPPER CERVICAL GANGLION) AND PARASYMPATHETIC SYSTEM (CILIARY GANGLION)
  - PARTICIPATE IN THE REGULATION OF CORNEAL WOUND HEALING AND REEPITHELIALIZATION

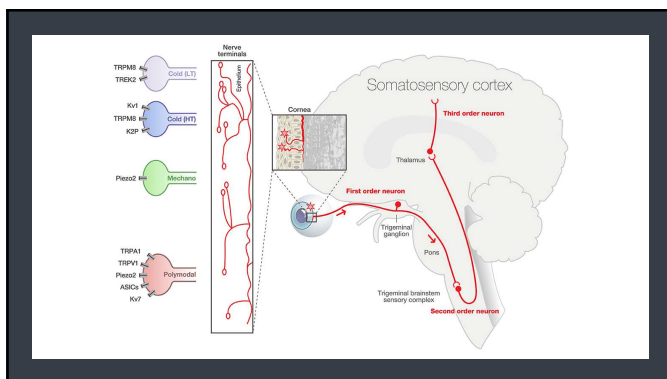
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### 3 DISTINCT CLASSES OF PERIPHERAL SENSORY NERVE FIBER OF THE CORNEA

| Receptor type        | Channel      | Stimulus                      | Clinical tie-in                |
|----------------------|--------------|-------------------------------|--------------------------------|
| Polymodal nociceptor | TRPV1, TRPA1 | Heat, chemicals, inflammation | Dry eye pain, neuropathic pain |
| Cold thermoreceptor  | TRPM8        | Cooling, evaporation          | Reflex tearing                 |
| Mechanoreceptor      | Piezo2       | Touch, injury                 | F8 sensation                   |

- MECHANO-NOCICEPTORS (A $\Delta$  FIBERS)**
- COLD RECEPTORS (A $\Delta$  AND C FIBERS) ARE ACTIVATED BY THERMAL CHANGES**
  - LOW BACKGROUND-HIGH THRESHOLD (LB-HT)
  - OCULAR SURFACE QUALITY, SMALL TEMP CHANGE
  - HIGH BACKGROUND-LOW THRESHOLD (HB-LT)
  - LARGER TEMP CHANGE
- POLYMODAL NOCICEPTORS (A $\Delta$  AND C FIBERS)**

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### NERVES, NERVES, NERVES

**Neuromediators**

- 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

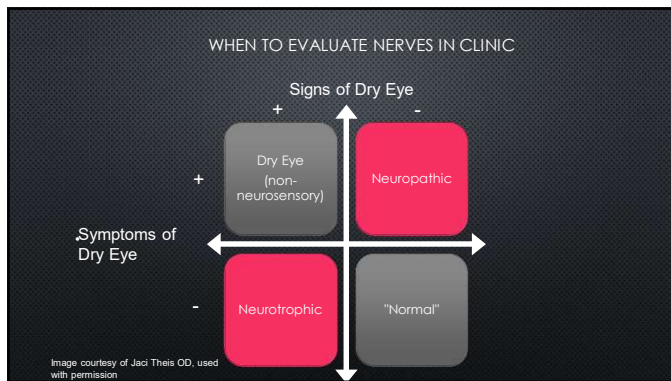
**Job #1:** react to injury at the ocular surface by registering pain and irritation and triggering protective reflexes, such as tear production and blinking

**Job #2:** release neuromediators that provide trophic support to corneal epithelial cells and keratocytes<sup>1,2</sup>

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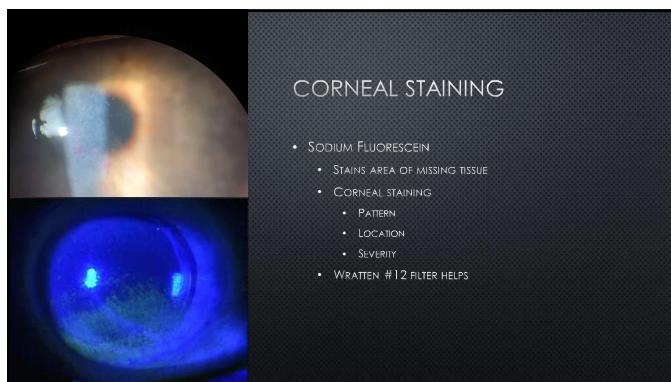
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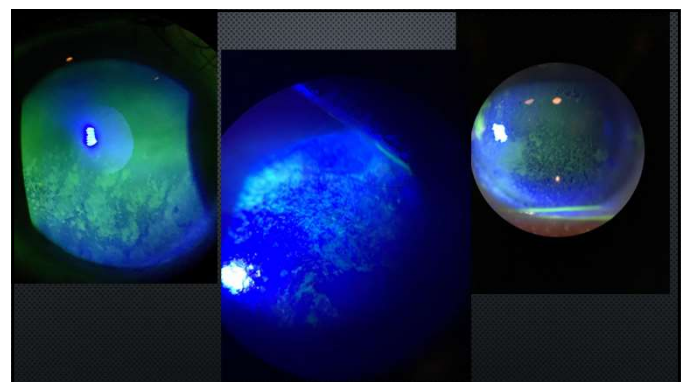
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- PAIN WITHOUT STAIN
- STAIN WITHOUT PAIN
- LIMBAL STEM CELL DEFICIENCY
- WHEN SOMETHING DOES MAKE SENSE
- HISTORY OF OCULAR SHINGLES
- HISTORY/CURRENT CHEMOTHERAPY
- HISTORY OF SYSTEMIC ISSUES
- HISTORY OF TBI
- AND MORE

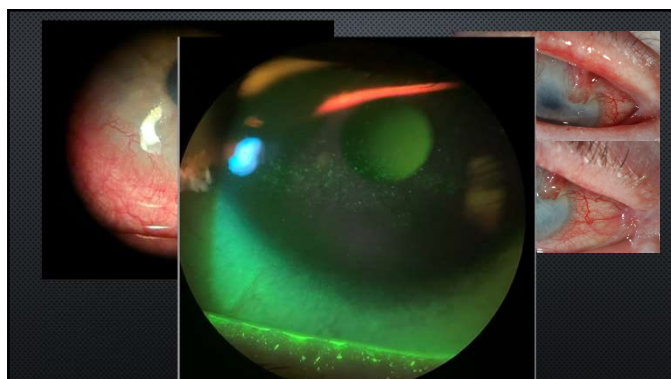
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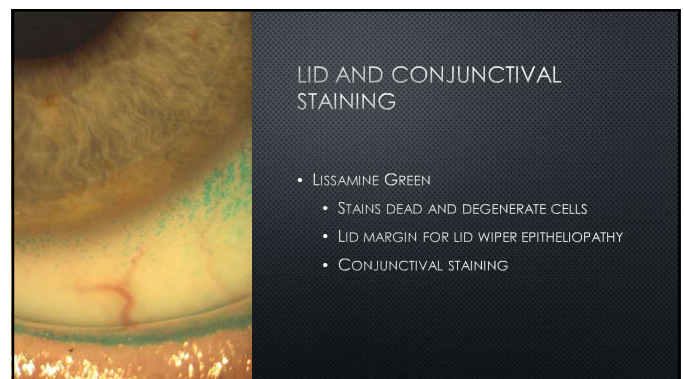
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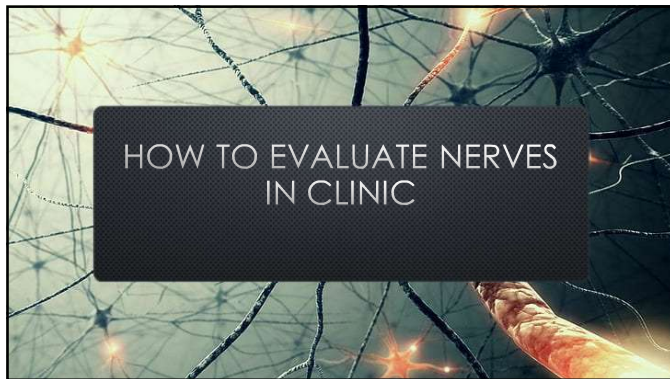
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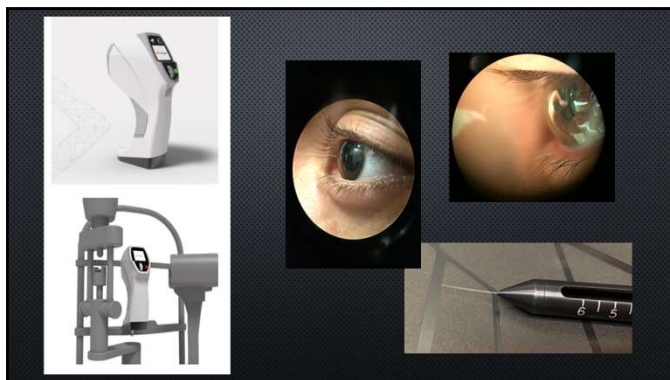


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### CORNEAL SENSITIVITY TESTING: ESTHESIOMETRY

- QUALITATIVE
  - COTTON TIP APPLICATOR
  - DENTAL FLOSS
  - TISSUE PAPER
- QUANTITATIVE
  - COCHET-BONNET
  - BELMONT NON CONTACT GAS ESTHESIOMETER
  - BRILL ESTHESIOMETER

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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. . .DO

- 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

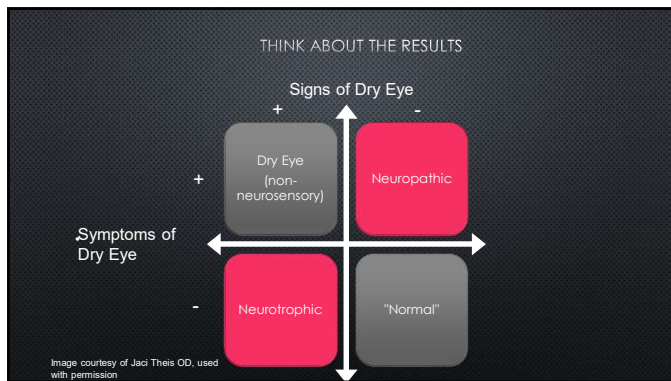
CNVII (8) Acoustic Nerve

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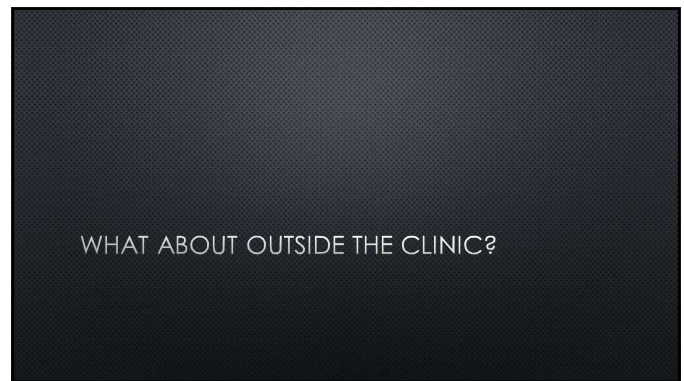
### PROPARACAINE CHALLENGE

- CENTRAL VS PERIPHERAL PAIN
- 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 THE OCULAR SURFACE.
    - 0.5% PROPARACAINE WITH HELP WITH PERIPHERAL PAIN (EYE IS A PERIPHERAL AREA) NOT WITH CENTRAL PAIN.

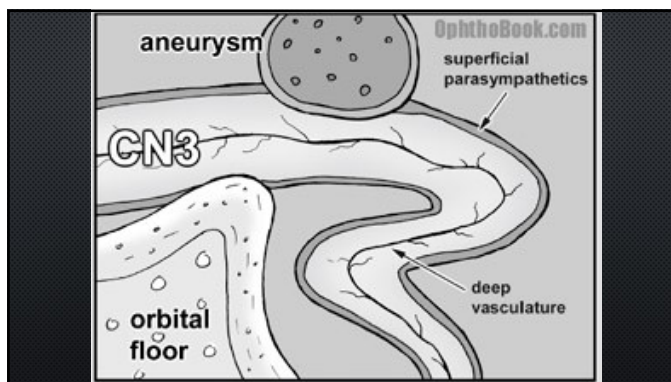
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HOW TO ORDER AN MRI

**MRI**

- Order an MRI of the head and orbits with and without contrast within a few weeks
- Consider neck as well
- Can be scheduled with out patient clinics or at MRI centers
- Your front desk staff can help the patient with this.

**MRA vs MRV**

- Artery vs veins
- Aneurysms, dissections, cerebral venous sinus thrombosis

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DETAILS TO CONSIDER

- MRI OF HEAD VS MRI OF ORBITS VS MRI OF NECK
  - DO YOU REALLY NEED BOTH?
  - WHEN SHOULD YOU ORDER BOTH?
- PREGNANCY OK BUT NO CONTRAST
- DO NOT ORDER IN PATIENTS WITH METAL IMPLANTS OR PINS, PACEMAKERS, OR IMPLANTED CARDIAC DEFIBRILLATORS
- CLAUSTROPHOBIA PATIENTS CONSIDER OPEN MRI IF OPTION
  - VALIUM HELPS

*Optic nerve sheath enhancement*

T1 MRI w/ contrast

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WHEN IS CT HELPFUL?

**Good to view**

- Bone abnormalities
- Calcification
- Bony involvement from soft tissue mass
- Metallic foreign bodies
- Fresh blood

**Indicated when:**

- Orbital trauma
- Proptosis, swelling of eyelids (orbital cellulitis, abscess, etc)
- Some instances MRI may still be preferred
- Intraocular or intraorbital foreign bodies
- Graves patients (can also use MRI)

**Avoid if possible in pregnant patients**

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## READING REPORTS

Procedures Performed: Exam  
MR MRV HEAD WWO Data/Time:  
CONTRAST 06/12/2021  
MR210621005305 3:36 PM

EXAM: MR MRV HEAD WWO CONTRAST

CLINICAL INDICATION/HISTORY: H47.013: Ischemic optic neuropathy, bilateral  
> Additional: Bilateral visual field defects, breast cancer

COMPARISON: None  
> Reference Exam: Brain MRI same day

TECHNIQUE: 2-D time of flight coronally acquired MRV was performed intracranially with multiple MIP reconstruction images obtained. Following gadolinium administration, fat saturated coronally acquired time-of-flight acquisition obtained with multiple MIP reconstructions obtained.

FINDINGS:  
Normal appearing superior and inferior sagittal sinuses, normal appearing bilateral transverse and sigmoid dural venous sinuses, left side slightly dominant. Visualized upper jugular veins unremarkable. No cortical venous abnormality.

IMPRESSION:  
Unremarkable brain MRV, no evidence of dural venous sinus thrombosis or stenosis.

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EXAM: MRI brain without and with gadolinium

CLINICAL INDICATION/HISTORY: H47.013: Ischemic optic neuropathy, bilateral  
> Additional: Bilateral visual field defects, breast cancer

COMPARISON: 8/13/2014  
> Reference Exam: None

TECHNIQUE: Sagittal FLAIR T1, axial T1, T2, FLAIR, T2 gradient, and diffusion sequences obtained of the brain. Following gadolinium administration, axial and coronal T1 sequences obtained. Additional axial T1 post gadolinium magnetization transfer sequence obtained. Imaging was performed on a 3 Tesla Siemens Magnetom Vida scanner.

FINDINGS:  
Diffusion: There are no areas of restricted diffusion, no evidence of an acute infarction.  
Brain parenchyma: New tiny chronic infarct posterior left cerebellum. Slight increased mild confluent and multifocal increased T2 and FLAIR signal periventricular and deep cerebral white matter including subcortical white matter. Stable small T2 hyperintense foci bilateral basal ganglia including likely chronic lacunar infarct lateral right basal ganglia. No cortical signal abnormality. No new mass hemorrhage edema or mass effect.  
Ventricles and sulci: Normal. No significant atrophy given age.  
Extra-axial: No extra-axial fluid collection or mass is noted.  
Contrast: There is no abnormal enhancement.  
Brain vasculature: No vascular abnormality is appreciated on this routine brain MR examination.  
Craniovertebral junction: Normal.  
Skull base, petrous temporal and zygomatic: Stable moderate retraction cyst or polyp inferior left maxillary sinus with bilateral lens implants, IACs and mastoid. MRVJ unremarkable. Stable mildly expanded paranasal sinuses. There is enhancing mild low T1 marrow signal lesion right posterior frontal skull near the vertex, 10 mm in diameter. No other discrete concerning skull lesion.

IMPRESSION:  
1. No evidence of acute infarct or other acute intracranial finding. No evidence of intracranial metastatic disease.  
2. New tiny chronic left cerebellar infarct. Small right basal ganglia chronic lacunar infarct. Slight progression of white matter signal changes likely chronic microvascular ischemic disease.  
3. 1 cm enhancing skull lesion posterior right frontal skull near the vertex, concerning for osseous metastatic lesion. Further evaluation nuclear medicine bone scan suggested to evaluate for other lesions.

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## BLOOD WORK: ORDER IT

- TSH/TSI/T3/T4
- ESR
- CRP
- TOTAL CBC
- SJO PANEL (SOME IN ENA PANEL)
- ANA
  - ORDER MORE SPECIFIC IF POSITIVE OR REFER OUT
  - EXTRACTABLE NUCLEAR ANTIGEN PANEL (ENA)
- HLA-B27
- ANCA
- RF
  - Anti-CCP TEST
- COMPLEMENTS: C3, C4, C5
- ANTI-DSDNA

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## WHAT HAPPENS WHEN A GOOD NERVE GOES BAD. . .

OR WHAT HAPPENS WHEN THE CORNEA LOOSES ITS NERVE? IS THAT BETTER?

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## WHEN TRIGEMINAL NERVE/CNV FUNCTION IS IMPACTED

- DECREASE LFU FUNCTION
  - DECREASED TEAR VOLUME
  - CHANGE TEAR BALANCE
- DECREASED BLINK RATE
- NEUROPATHIC CORNEAL PAIN
- NEUROTROPHIC KERATITIS
- SYMPTOMS
  - PAIN, ICH, BURNING
  - NOTHING
  - LIGHT SENSITIVITY
  - VISUAL SNOW
  - INCREASE IN MIGRAINES
  - BLEPHAROSPASM

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## THINGS THAT CAN AFFECT NEUROLOGICAL FUNCTION

- AUTOIMMUNE DISORDERS
- VIRUSES
  - COVID
  - GBS
  - HERPES
- TUMORS, MASS, LESIONS
- CHRONIC INFLAMMATION
- PHYSICAL DAMAGE
- TRAUMATIC BRAIN INJURY
  - THYROID CHANGES?

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Slide 41

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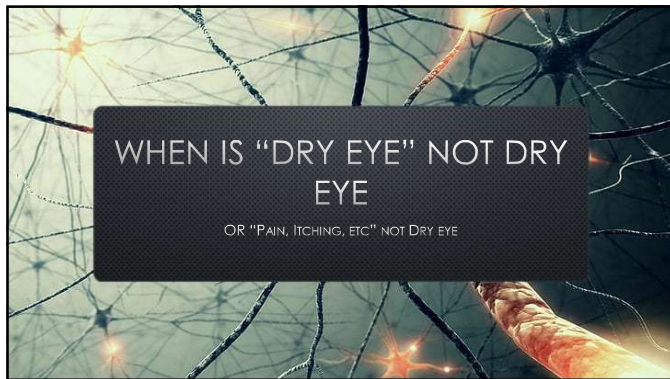
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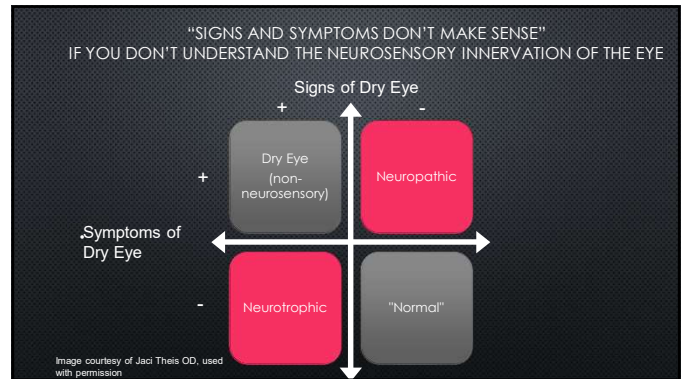
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### TRIGEMINAL NEUROPATHY

- GENERAL TERM FOR DYSFUNCTION IN SENSORY OR MOTOR FUNCTIONS INVOLVING CNV
- TYPICALLY NUMBNESS IN REGION OF INNERVATION OF CNV
  - SOMETIMES WITH PARAESTHESIAS, PAIN OR MASTICATORY WEAKNESS
  - CAN OCCUR ANYWHERE WITHIN THE NERVE COURSE
- PAIN IS USUALLY CONTINUOUS, BURNING OR SQUEEZING AND COMES WITH ALLODYNIA AND COLD HYPERALGESIA
- RULE OUT POTENTIALLY HARMFUL UNDERLYING CONDITIONS

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### PATIENTS WITH TNO USUALLY COMPLAIN OF ONE OF THE FOLLOWING SYMPTOMS:

- HYPOESTHESIA—PARTIAL LOSS OF SENSATION IN THE DISTRIBUTION OF THE AFFECTED NERVE.
- ANESTHESIA—COMPLETE LOSS OF SENSATION IN THE DISTRIBUTION OF AN AFFECTED NERVE.
- HYPERESTHESIA—ABERRANT DISCOMFORT (SUCH AS BURNING, ITCHING, OR RARELY PAIN), WHICH IS PERCEIVED ALONG WITH DECREASED OR LOSS OF SENSATION IN THE DISTRIBUTION OF THE AFFECTED NERVE

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### TRIGEMINAL NEURALGIA

- MOST COMMON CRANIOFACIAL NEURALGIA
- RECURRENT UNILATERAL BRIEF ELECTRIC SHOCKLIKE PAINS
  - ABRUPT IN ONSET AND TERMINATION
  - LIMITED TO DISTRIBUTION OF ONE OR MORE DIVISIONS OF TRIGEMINAL NERVE AND TRIGGERED BY INNOCUOUS STIMULI
- UP TO 30% OF PATIENTS MAY PRESENT WITH MODERATE CONTINUOUS PAIN IN SAME DISTRIBUTION AS AFFECTED NERVE DIVISION

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### 3 MAIN TN CATEGORIES

- CLASSIC
  - ASSOCIATED WITH NEOVASCULAR COMPRESSION OF TRIGEMINAL NERVE ROOT WITH ASSOCIATED MORPHOLOGIC CHANGES ON MRI
- SECONDARY/SYMPOMATIC (STN)
  - ASSOCIATED WITH UNDERLYING DISEASE SUCH AS MS, SPACE OCCUPYING LESION, DURAL ARTERIOVENOUS FISTULAE OR GENETIC CAUSES
- IDIOPATHIC (ITN)
  - DIAGNOSIS OF EXCLUSION

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## DIAGNOSTIC CRITERIA

- RECURRENT UNILATERAL FACIAL PAIN IN ONE OR MORE DISTRIBUTIONS OF THE TRIGEMINAL NERVE WITH NO RADIATION BEYOND AND FULFILLING CRITERIA B AND C
- PAIN HAS THE FOLLOWING CHARACTERISTICS:
  1. LASTS FROM A FRACTION OF A SECOND TO 2 MINUTES
  2. SEVERE INTENSITY
  3. ELECTRIC SHOCKLIKE, SHOOTING, STABBING, OR SHARP IN QUALITY
- PRECIPITATED BY INNOCUOUS STIMULI WITHIN THE AFFECTED TRIGEMINAL DISTRIBUTION
- IS NOT ACCOUNTED FOR BY ANOTHER [ICHD-3 DIAGNOSIS]

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## TRIGEMINAL NEUROPATHIC PAIN IS DIFFERENT FROM TRIGEMINAL NEURALGIA.

TRIGEMINAL NEURALGIA (TN) IS A SPECIFIC, SEVERE TYPE OF **NEUROPATHIC PAIN** CHARACTERIZED BY STABBING, ELECTRIC SHOCK-LIKE FACIAL SPASMS. WHILE ALL TN IS NEUROPATHIC PAIN, NOT ALL NEUROPATHIC PAIN IS TN

56

## FURTHERMORE

- **TRIGEMINAL NEURALGIA** AND **CORNEAL NEUROPATHIC PAIN** BOTH INVOLVE THE TRIGEMINAL NERVE BUT DIFFER IN LOCATION AND SENSATION.
- TN CAUSES SEVERE, STABBING, ELECTRIC-SHOCK PAINS IN THE FACE, JAW, OR EYE AREA
- CNP CAUSES CHRONIC, BURNING, FOREIGN-BODY SENSATIONS STRICTLY IN THE EYE.

57

## TRIGEMINAL HYPOESTHESIA OR ANESTHESIA: NEUROTROPHIC KERATITIS

58

## Corneal Nerve Damage is Central to NK

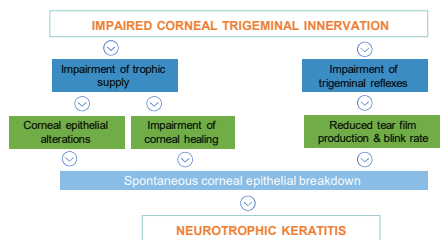


Image courtesy of John Attalla, MD

59

## 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



### CNS

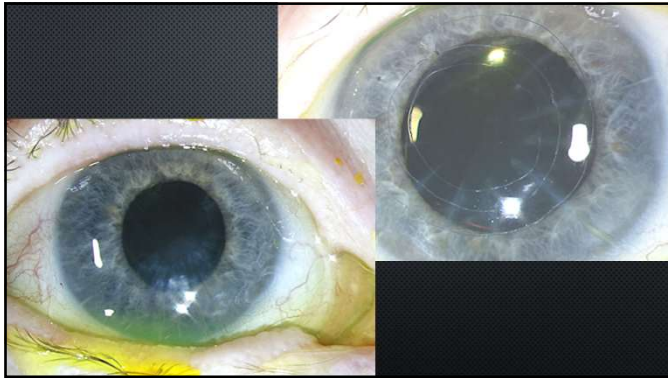
- Neoplasm
- Aneurysms
- Stroke
- TBI/TBSI
- Degenerative disorders of the CNS
- Neurosurgical procedures
- Congenital/developmental malformations (eg, trigeminal nerve hypoplasia)

### IATROGENIC

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

CNS, central nervous system.  
Dua HS et al. *Prog Retin Eye Res.* 2018;66:107-131. Semeraro F et al. *Ophthalmologica.* 2014;231(4):191-197.

60

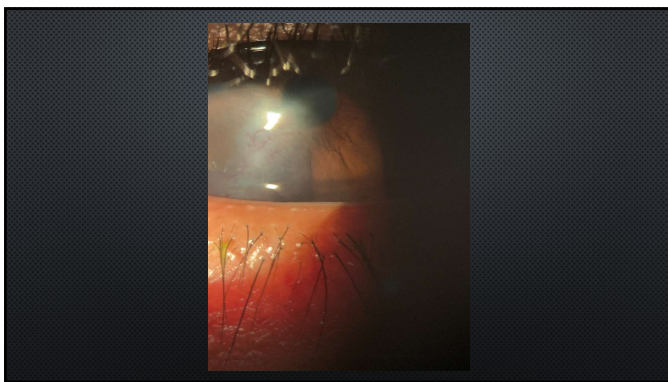


61

### PT #1 DUDE, WHATS THIS WHITE SPOT

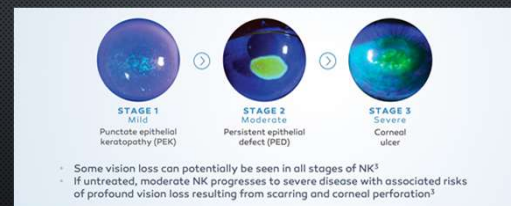
- 32 YEAR OLD WHITE MALE
- PRESENTS BECAUSE HAS A WHITE SPOT ON HIS EYE OD. HABITUALLY SLEEPS IN CL AND EVERY FEW MONTHS HE WILL HAVE SIGNIFICANT PAIN IN HIS EYE. USUALLY GOES IN DARK ROOM FOR A DAY AND SLEEPS AND ITS BETTER. THIS OCCURRED 3 DAYS AGO AND THIS TIME IT DID NOT GET BETTER AND NOW HAS A WHITE SPOT. ALWAYS HIS OD
- OD CORNEAL EDEMA, STROMAL NEOVASC, SCARRING LIKELY, ALL EXTENDING INTO VISUAL AXIS.
- LIKELY HAS BEEN EXPERIENCING HSV FLARES AND HAS AN ACTIVE HSV DISCIFORM.
- PT STARTED ON TOPICAL STEROID/ ANTIBIOTIC AND ORAL ANTIVIRAL
- RTC 1 WEEK IMPROVED, KEPT ON STEROID AND ANTIVIRAL
- 1 MONTH FU RECEDING NEOVASC, REFERRED FOR POSSIBLE CORNEAL AVASTIN INJECTION/PTK AS WELL AS SCLERAL CL FIT.
- 6 MONTH FU BCVA IMPROVED TO 20/30, GHOST VESSELS IN STROMA, NO REOCCURRENCE. DEFERRED FIT IN SCLERAL AND IS NOT WANTING TO RETURN TO CL USE AT ALL.

62



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### MACKIE CLASSIFICATION



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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 |

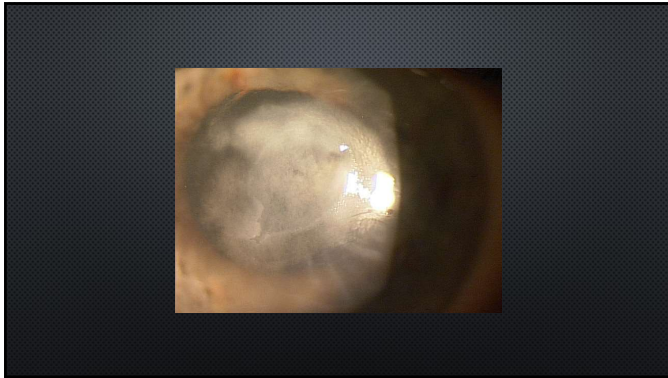
Neurotrophic Keratopathy Study Group. *Ocul Surf*. 2023;30:129-138

65

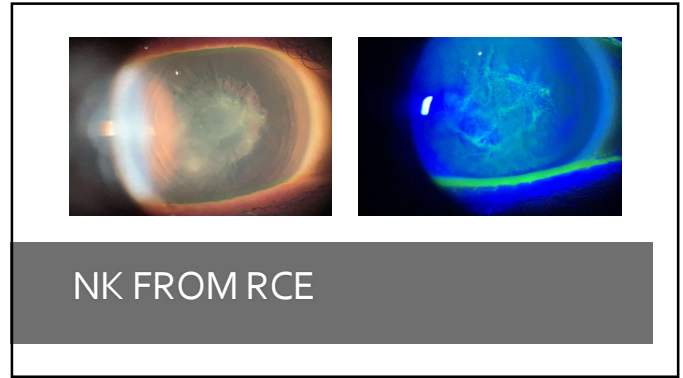
### PT # THE HAT TRICK

- 45YEAR OLD ASIAN FEMALE
- PRESENTS FOR CORNEAL ABRASION, DIAGNOSED WITH RCE
- RTC 1 WEEK FU
  - UNHEALING CORNEAL DEFECT
  - STROMAL HAZE
  - HSV FLARE, STARTED ON ANTIVIRALS
- F/U → IMPROVES OVER 2 WEEKS BUT CORNEAL DEFECT AND HAZE STILL PERSISTENT
  - CORNEAL SENSITIVITY TESTING, 100% DESENSITIZED, NOW HAS NK
  - AM MEMBRANE, CYCLOSPORINE, VIT A UNG, CORTICOSTEROIDS
    - NO IMPROVEMENT, MOVED TO OVERVATE
    - WHEN STABLE REFERRED FOR SCLERAL LENS FIT AND DALK/PK CONSULT WITH CORNEA

66



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NK FROM RCE

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## ONGOING NK/PCED TREATMENT STUDIES

| Company       | Trial        | Stage                                                                        |               |
|---------------|--------------|------------------------------------------------------------------------------|---------------|
| Kala/Combango | KP-012-C-001 | Failed to meet primary and secondary endpoints in the phase 2b test for PCED | Oct 2025      |
| Claris Bio    | CSS-001      | Phase 2 enrolled complete, no readout                                        | Summer 2024   |
| RegenEx/HLB   | RGN-259      | Phase 3 Complete, failed to meet primary endpoint                            | July 2025     |
| BRIM          | BRM-024      | Phase 2 complete                                                             | November 2025 |
| Novame        | ST266        | Phase 2 complete                                                             | 2022          |

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## TREATMENT

- MANAGE OSD
  - OMEGA 3 FA, LID HYGIENE
  - PFAT
  - MGD MANAGEMENT
  - THBL, SCLERALS
- ANTI-INFLAMMATORY
  - IMMUNOMODULATORY
  - CORTICOSTEROID
  - TACROLIMUS 0.3% (OINTMENT/DROP)
  - AMNIOTIC MEMBRANE
- NEUROREGENERATIVE
  - AUTOLOGOUS SERUM, PRP, PRGF
  - TOPICAL INSULIN?
  - CENEGERMIN
- SYSTEMIC
  - GABAPENTIN, CARBAMAZEPINE, PREGABALIN
  - LOW DOSE NALTREXONE 1.5MG AT BED
  - TCA 10-15MG BED
  - TRAMADOL
  - VITAMIN B

70

## UNIVERSITY OF ALBERTA TOPICAL INSULIN

Chen et al. BMC Ophthalmology (2024) 24:155  
<https://doi.org/10.1186/s12886-024-03450-3> BMC Ophthalmology

RESEARCH Open Access

**Insulin eye drops improve corneal wound healing in STZ-induced diabetic mice by regulating corneal inflammation and neuropeptide release**

Shudi Chen<sup>1†</sup>, Yingli Li<sup>1†</sup>, Wenjing Song<sup>1</sup>, Yu Cheng<sup>1</sup>, Yuan Gao<sup>1</sup>, Luoying Xie<sup>1</sup>, Meiling Huang<sup>1</sup> and Xiaoming Yan<sup>1\*</sup>

**Abstract**

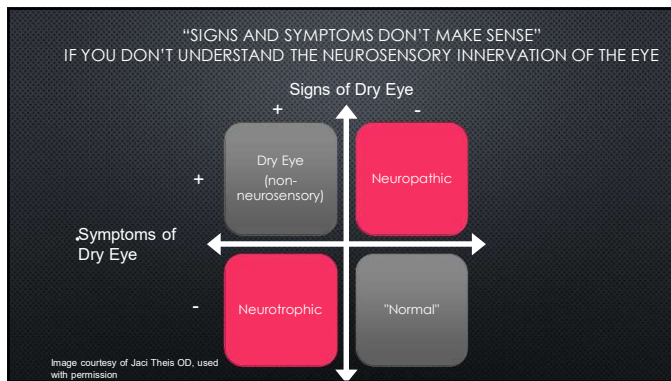
**Introduction:** Insulin eye drops have attracted increasing attention from researchers and

71

## 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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### NEUROPATHIC CORNEAL PAIN OR ITCH

- REMEMBER: NP = PAIN INITIATED AS A DIRECT CONSEQUENCE OF A LESION OR DISEASE AFFECTING THE SOMATOSENSORY SYSTEM IN EITHER THE PNS OR CNS
- NCP OCCURS IN THE CORNEA AS CONSEQUENCE OF DAMAGE OR DISEASE AFFECTING THE CORNEAL NERVES, PERIPHERAL TERMINALS OF THE TRIGEMINAL GANGLION NEURONS AND PART OF THE SOMATOSENSORY SYSTEM
- SUBJECTIVE SYMPTOMS OF PAIN, HYPERALGESIA, PHOTOALLODYNIA (PAINFUL SENSITIVITY TO LIGHT), PERSISTENT UNPLEASANT SENSATION (BURNING DRYNESS FBS)
  - NOT NECESSARILY VERIFIED BY OBJECTIVE CLINICAL SIGNS

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### NCP DIAGNOSIS

- SUGGESTED THAT THERE IS USUALLY
  - HISTORY OF LESION OR DISEASE OF THE CORNEAL NOCICEPTIVE PATHWAY
  - POSITIVE FINDINGS CORNEAL CONFOCAL BIOMICROSCOPY (CHANGES IN NERVE MORPHOLOGY)
  - PERSISTENCE OF SYMPTOMS AFTER INSTILLATION OF TOPICAL ANAESTHESIA
  - ABNORMAL RESPONSE TO TOPICAL INSTILLATION OF HYPEROSMOLAR DROPS (HYPERSENSITIVE TO 5% SODIUM CHLORIDE)
  - ABSENCE OF CLINICAL SIGNS OR PERSISTS AFTER TREATMENT OF OSD/OCULAR SURFACE ABNORMALITIES
- BUT ALSO:
  - PAIN CO-MORBIDITIES LIKE FIBROMYALGIA OR OCULAR SURFACE PAIN AFTER TRAUMA OR SURGICAL INJURY
  - ALLODYNIA -TYPE OF **NEUROPATHIC PAIN** WHERE A NORMALLY NON-PAINFUL STIMULUS, SUCH AS LIGHT TOUCH, A FEATHER, OR A MILD TEMPERATURE CHANGE, TRIGGERS A SENSATION OF PAIN
  - INCREASED OR DECREASED CORNEAL SENSATION

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### WHAT CAUSES THIS?

- COMORBIDITIES
  - DIABETES WITH DN, SPINAL CORD INJURY, MS, TRIGEMINAL NEURALGIA, IBS, LONG COVID, BURNING MOUTH SYNDROME, CHEMO
  - SYSTEMIC DISEASE (E.G., AUTOIMMUNE OR INFLAMMATORY CONDITIONS, DIABETES, FIBROMYALGIA)
  - OTHER NEUROLOGICAL DISEASE (E.G., TRIGEMINAL NEURALGIA, MIGRAINE)
  - DEPRESSION, ANXIETY
- 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)

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### REMEMBER PROPARACAINE TEST?

- HELPS TO DIFFERENTIATE BETWEEN PERIPHERAL AND CENTRAL NEUROPATHIC PAIN
- PEOPLE WHO EXPERIENCE TOTAL OR SOME RELIEF WITH PROPARACAINE CHALLENGE HAVE PERIPHERAL OR MIXED COMBINED CORNEAL NEUROPATHIC PAIN

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### 70 YEAR OLD MALE

- EXCRUCIATING OCULAR PAIN BOTH EYES THE LAST 6 MONTHS.
- PRESENTING FOR 3<sup>RD</sup> OPINION.
- OCULAR EXPOSURE TO DERMALOGICA<sup>PRO</sup> PRECLEANSE AT HAND & STONE DENVER ON MAY 8, 2023. TO MY KNOWLEDGE, THE PATIENT DID NOT RECEIVE AN EYEWASH OR IRRIGATION UNTIL MAY 11, 2023.
  - SOME INITIAL STAINING SEEN AT THAT TIME CORNEA AND CONJ (INITIAL EXAM NON-EYECARE PROFESSIONAL)

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## MY EXAM

- NO STAINING
- SIGNIFICANT DISCOMFORT AND SEVERE LIGHT SENSITIVITY
- COGNITIVE ISSUES BROUGHT HIS BROTHER BECAUSE IN SO MUCH PAIN COULDN'T CONCENTRATE
- COCHET-BOHNETT
  - SIGNIFICANT DECREASE IN CORNEAL SENSITIVITY FROM NORMAL IN 2 OUT OF 3 AREAS TESTED IN BOTH EYES.
- BUT ALSO HISTORY OF CHRONIC PAIN AND OPIOID USE FOR CONTROL

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## FAST FORWARD 8 MONTHS

- AUTOLOGOUS SERUM 40%
- LOTEPREDNOL QD (PREVIOUS PF COMPOUNDED DEX)
- EYELID HYGIENE
- COLD COMPRESSES
- OMEGA3, VITAMIN B, VITAMIN C, VIT D
- BUT WE ALSO TRIED/USED:
  - PUNCTAL PLUGS
  - AMNIOTIC MEMBRANES
  - CYCLOSPORINE
  - LIFEGRAST
  - ETC
- CORNEAL SENSATION BACK TO 5 OU ALL QUADRANTS
- NO LIGHT SENSITIVITY, CAN FUNCTION, IS ON HIS OWN
  - VERY SENSITIVE AND PRONE TO FLAKES WITH CHANGES IN WEATHER

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## TREATMENT

- MANAGE OSD
  - OMEGA 3 FA, LID HYGIENE
  - PFAT
  - MGD MANAGEMENT
  - THBL, SCLERALS
- ANTI-INFLAMMATORY
  - IMMUNOMODULATORY
  - CORTICOSTEROID
  - TACROLIMUS 0.3% (OINTMENT/DROP)
  - AMNIOTIC MEMBRANE
- NEUROGENERATIVE
  - AUTOLOGOUS SERUM, PRP, PRGF
  - TOPICAL INSULIN?
  - CONEGERMIN
- SYSTEMIC
  - GABAPENTIN, CARBAMAZEPINE, PREGABALIN
  - LOW DOSE NALTREXONE 1.5MG AT BED
  - TCA 10-15MG BED
  - TRAMADOL
  - VITAMIN B

81

## NEUROPATHIC PAIN: OKYO

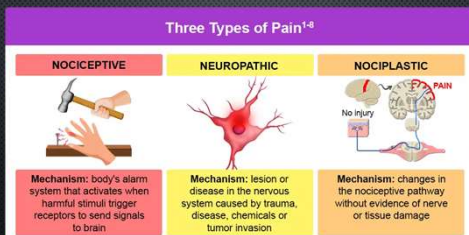
### OKYO Pharma Announces New Data Showing Favorable Corneal Nerve Outcomes in Phase 2 Study for Neuropathic Corneal Pain

Dec 11, 2020

- Patients treated with 0.05% icosonimod demonstrated directionally favorable improvements in nerve fiber count and fiber length, trends not observed in the placebo group
- These findings suggest that icosonimod may have a positive impact on corneal nerve health in patients with neuropathic corneal pain
- Corneal nerve imaging data from the Phase 2 NCP trial were analyzed using in vivo confocal microscopy

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- NOCICEPTIVE: "SOMETHING IS DAMAGING MY TISSUES."
- NEUROPATHIC: "MY NERVES ARE DAMAGED."
- NOCIPLASTIC: "MY CENTRAL NERVOUS SYSTEM IS PROCESSING PAIN INCORRECTLY."



83

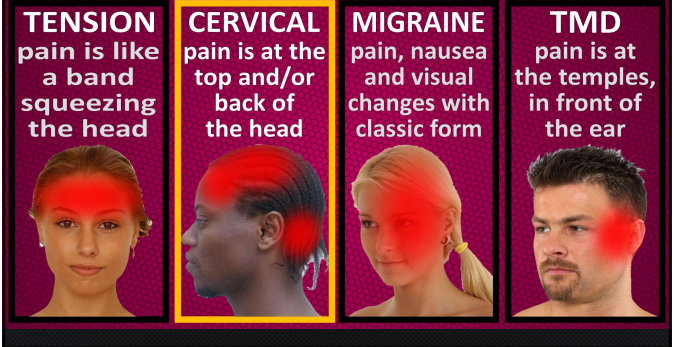
## CERVICOGENIC REFERRED PAIN

84

### 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?
  - SACCADEIC EYE MOVEMENT
    - NECK MUSCLES ENGAGE TO KEEP HEAD STILL WHILE EYES MOVE FOR SACCADDES
    - IF SOMEONE HAS A NECK INJURY TO THESE SUPPORTING MUSCLES, WHEN A PATIENT USES A LOT OF SACCADDES DOING VISUAL TASKS CAN TRIGGER PAIN
  - SENSORY NERVES IN THE NECK OVERLAP WITH SOME TRIGEMINAL SENSORY NERVES OF THE EYE
    - TRIGGER POINTS

85



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**Table 1 – Major diagnostic criteria of cervicogenic headache, as set forth by the Cervicogenic Headache International Study Group<sup>13</sup>**

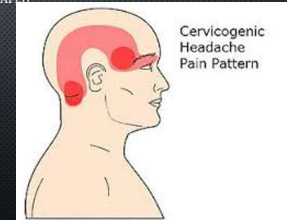
- Evidence of cervical involvement
  - Pain precipitated by neck movement, sustained neck position, and/or external pressure on neck structures
  - Restricted cervical range of motion
  - Ipsilateral neck, shoulder, and/or arm pain
- Pain relief with anesthetic nerve blockade
- Unilateral head pain, without side shift

Strict fulfillment of criterion I requires that point (a) be present, although points (b) and (c) together provisionally fulfill criterion I. Fulfilling criteria I and II is required for the diagnosis of cervicogenic headache. Fulfilling criteria I, II, and III is preferred for scientific study of cervicogenic headache.

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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



88

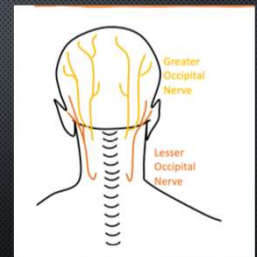
### 47 YEAR OLD MALE

- "MY EYES HURT WHEN I TRY TO READ ESPECIALLY ON COMPUTER. "
- BETTER IF WEARING GLASSES WITH HIS CONTACTS
- MINIMAL OSD, BUT DOES HAVE DECREASED CORNEAL SENSATION
  - NK WITH NEUROPATHIC PAIN?!
- TREAT OSD AND CORNEAL FUNCTION WITH AUTOLOGOUS SERUM FOR 8 MONTHS
  - CORNEAL SENSATION NORMAL! EYE ASENTHOPIA WHEN NOT ON COMPUTER 100% BETTER. . .
  - BUT NOT WHEN ON COMPUTER OR READING
- ASKED, HAS CERVICOGENIC NECK ISSUES
  - DISCUSSED ERGONOMICS WHILE WORKING AND TRAVELING REFERRED OUT TREATED WITH OT/PT AND MASSAGE THERAPY

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### OCCIPITAL NEURALGIA

- HEADACHES CAUSED BY IRRITATION TO GREATER OR LESSER OCCIPITAL NERVE
- WHERE IS LOCATION OF PAIN?
  - BACK OF HEAD, NECK, SCALP, FOREHEAD, BEHIND EYES
- TYPE OF PAIN
  - BURNING, HOT, ELECTRIC LIKE, INTENSE, STABBING, BRIEF OR CHRONIC
  - 2NDARY SYMPTOMS: VISION/OCULAR PAIN (67%), TINNITUS (33%), DIZZINESS (50%), NAUSEA (50%)
- PILLOW SIGN:
  - PAIN WITH LYING ON PILLOW IN SUPINE WITH HYPEREXTENSION OR ROTATION OF HEAD



Picture courtesy of Joel Thies

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## TREATMENT

- **Non-Surgical Treatments**
- **Medications:** NSAIDs (ibuprofen, naproxen) to reduce inflammation, muscle relaxants to ease spasm-induced compression, and anti-seizure or antidepressant medications to manage nerve pain.
- **Injections (Nerve Blocks):** Injections of a local anesthetic and, in some cases, steroids, are placed around the occipital nerves to block pain signals and reduce inflammation, providing temporary to long-lasting relief.
- **Botox Injections:** Used to reduce nerve inflammation, particularly when other treatments fail.
- **Physical Therapy:** Techniques include manual therapy, massage, and postural exercises to reduce muscle tension.
- **At-Home Care:** Applying a warm compress to the base of the head/neck to relax muscles and reduce pain.
- **Surgical Interventions**
- **Occipital Nerve Stimulation:** A device, similar to a pacemaker, is implanted under the skin to send low-voltage electricity to the occipital nerves to disrupt pain signals.
- **Spinal Cord Stimulation:** Electrodes are placed near the spinal cord to manage pain.
- **Decompression Surgery:** Procedures aimed at relieving pressure on the affected occipital nerves.

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## CERVICOGENIC VS OCCIPITAL

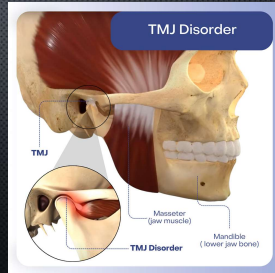
- BOTH NECK-RELATED PAIN CONDITIONS THAT CAN OVERLAP.
- DIFFER IN NERVE INVOLVEMENT AND PAIN QUALITY.
- CN INVOLVES IRRITATION OF THE GREATER/LESSER OCCIPITAL NERVES.
  - CAUSING SHARP, ELECTRIC-SHOCK PAIN.
- CGH ORIGINATES FROM CERVICAL SPINE PATHOLOGY (JOINTS/DISCS)
  - CAUSING DULL, ACHING HEAD PAIN.

| Key Differences at a Glance |                                            |                                                     |
|-----------------------------|--------------------------------------------|-----------------------------------------------------|
| Feature                     | Occipital Neuralgia (ON)                   | Cervicogenic Headache (CGH)                         |
| Primary Mechanism           | Injury/compression of the occipital nerves | Referred pain from upper cervical spine (C1-C3)     |
| Pain Quality                | Sharp, shooting, electric-shock, stabbing  | Dull, aching, throbbing                             |
| Pain Location               | Base of head, radiates over scalp          | Neck, radiating to forehead (posterior-to-anterior) |
| Key Trigger                 | Touching scalp, brushing hair              | Neck movement, sustained posture                    |
| Associated Symptoms         | Numbness, scalp tenderness                 | Reduced range of motion (neck), nausea              |

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## SPEAKING OF BOTOX AND PAIN? . . . WHAT ABOUT TMJ?

- TMJ DISORDERS CAN CAUSE NEUROPATHIC PAIN WHEN INFLAMMATION OR MISALIGNMENT COMPRESSES NEARBY NERVES, PARTICULARLY THE TRIGEMINAL NERVE.
- **SYMPTOMS OF TMJ-RELATED NEUROPATHIC PAIN**
  - **Facial Pain & Numbness:** Sharp, burning, or tingling sensations, or "pins and needles".
  - **Headaches & Migraines:** Often tension-type, originating in the jaw area.
  - **Ear Symptoms:** Ringing (tinnitus), fullness, or earaches.
  - **Muscle Spasms:** Involuntary twitching of facial muscles.
  - **Neck & Shoulder Pain:** Referred pain or stiffness due to muscle tension.



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## TMJ Disorder - Pain associated CAUSES AND MECHANISMS

- **Nerve Compression:** A misaligned TMJ can press on nearby nerves, especially the trigeminal nerve.
- **Proximity:** A shorter distance between the TMJ disk and the mandibular nerve can increase neuropathic pain risk, possibly from direct compression, traction, or friction during jaw movement.
- **Central Sensitization:** TMJ issues can alter pain processing in the brain, making it more sensitive to pain signals, a feature of neuropathic pain.

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## WAIT WHAT ELSE DOES THIS STUFF DO?!

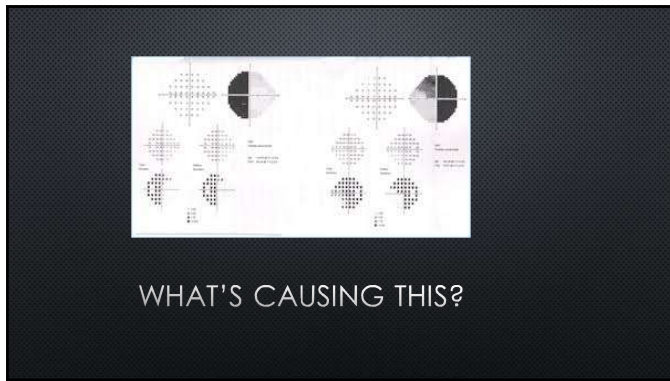
- FINE LINES AND WRINKLES, . . .
- MIGRAINES
- INFERIOR INCOMPLETE LID CLOSURE (SOMETIMES)
- BLEPHAROSPASM

95

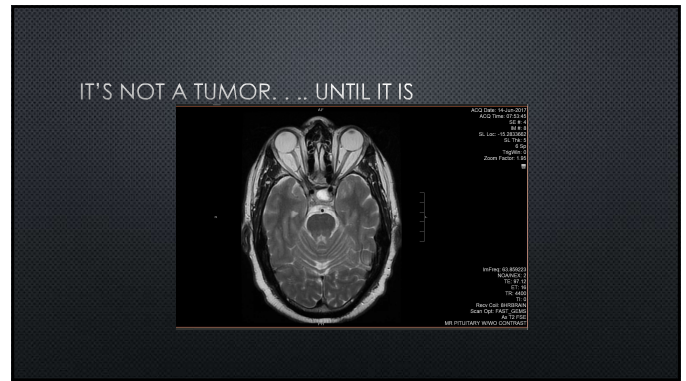
## CONJUNCTIVOCHALASIS WITH OR WITHOUT MICROBLEPHAROSPASM

- BLINKING WITH MECHANICAL RUBBING CAUSES IRRITATION AND INFLAMMATION
- OCULOPLASTICS?
  - FUNCTIONAL BOTOX? (OUR GOOD FRIEND)
  - SURGICAL RESECTION OF CONJUNCTIVA
  - PLASMA PEN?

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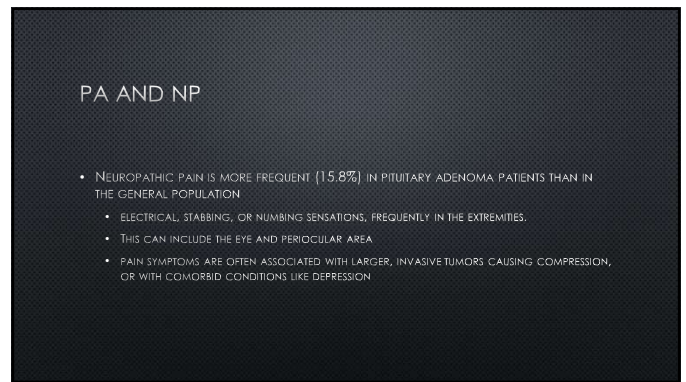
97



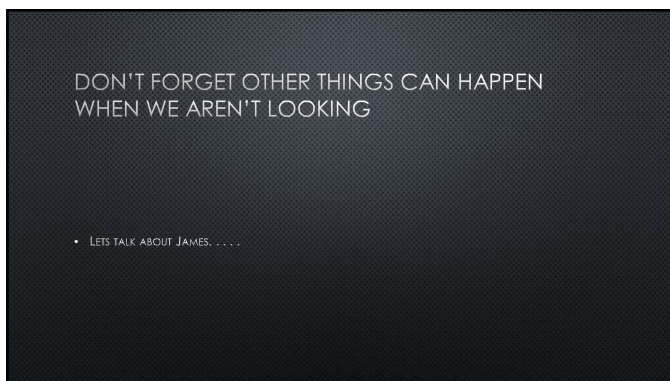
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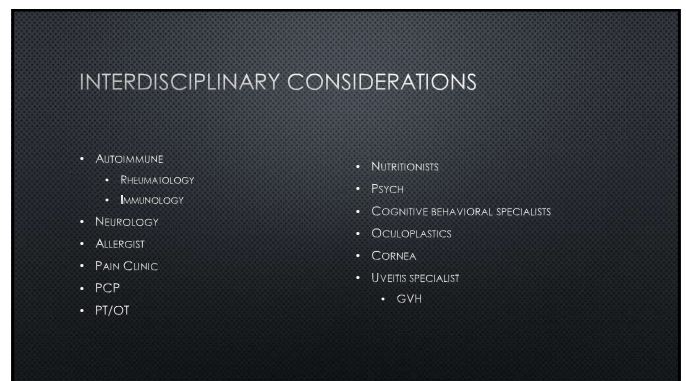
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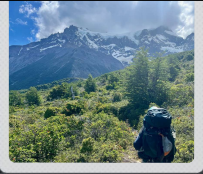


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### TAKE AWAY:

- EVEN WHEN YOU THINKS IT NOT NEURO, IT IS
  - THE EYE IS A NEUROLOGICAL EXTENSION
- PAIN IS TELLING A STORY, WE JUST HAVE TO LISTEN
- WE CAN OFFER A LOT MORE HELP THAN WE REALIZE.

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QUESTIONS?  
DR.CECELIAKOETTING@GMAIL.COM  
W TREK PATAGONIA CHILE AND ARGENTINA 2025

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