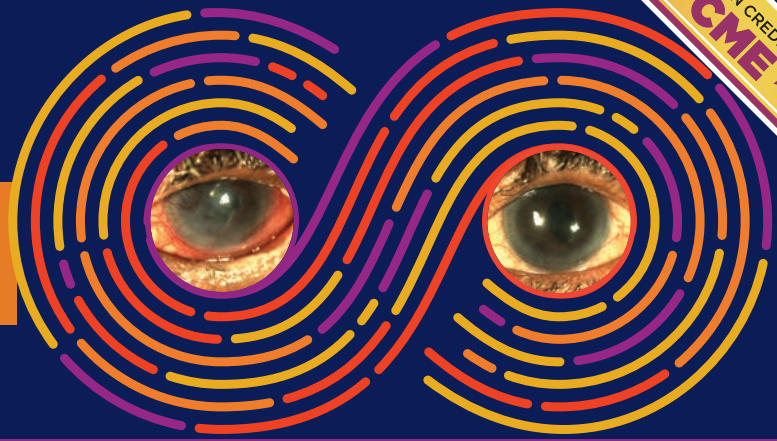
CME MONOGRAPH

ReNewed Sensation

IMPROVING AWARENESS, DIAGNOSIS, AND TREATMENT OF NEUROTROPHIC KERATITIS



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ACTIVITY DESCRIPTION AND PURPOSE

Neurotrophic keratitis (NK) is characterized by disrupted tearing and progressive corneal damage that does not readily heal. Until very recently, a lack of approved treatments to reinnervate and heal eyes affected by NK served to further hamper efforts toward timely diagnosis. Now that an approved therapeutic agent is available, ophthalmologists are better armed to identify patients with early stages of NK and to better strategize individual treatment regimens before the disease progresses to the point of corneal perforation and subsequent loss of visual acuity. This supplement is based on the proceedings of a virtual symposium that took place on November 13, 2020. The desired results of this educational activity are for ophthalmologists to have a better understanding of the pathophysiology of NK, newly developed disease stage classification, and current best practices for screening, diagnosis, and treatment.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

After completing this activity, participants will be better able to:

- Describe the pathophysiology of neurotrophic keratitis
- Integrate evaluation of corneal sensitivity into assessment of ocular surface disease
- Review evidence of corneal healing and reinnervation in patients treated with recombinant human nerve growth factor
- Identify treatment strategies for patients diagnosed with any stage of neurotrophic keratitis

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ReNewed Sensation

IMPROVING AWARENESS, DIAGNOSIS, AND TREATMENT OF NEUROTROPHIC KERATITIS

Introduction

Neurotrophic keratitis (NK) is a potentially sight-threatening condition characterized by decreased or absent corneal sensitivity. Given that NK has been considered a rare disease, its diagnosis in many patients with early findings may be overlooked. Consequently, NK may be more common than previously appreciated. Early recognition of NK with initiation of appropriate therapy is important to mitigate progression to later stages that are associated with irreversible tissue damage and vision loss. An approved medical treatment that addresses the underlying pathophysiology of NK is now available to treat all stages of the disease.

Pathogenesis, Etiology, and Classification

Edward J. Holland, MD

Pathogenesis

Neurotrophic keratitis is defined as dysfunction of corneal innervation that results in dysregulation of corneal and/or cellular function (Neurotrophic Keratitis Study Group, unpublished report, 2020). It is characterized by a loss of corneal sensation and neuronal homeostasis, which leads to eventual corneal epithelial breakdown and, ultimately, keratolysis if untreated. The altered corneal sensation leads to loss or imbalance of trophic factors that support the corneal epithelium and corneal nerves as well as secondary alterations of the components of the lacrimal functional unit, which includes the cornea, conjunctiva, meibomian glands, eyelids, and the sensory and motor nerves that connect them. Collectively, these changes result in the clinical manifestations of NK, such as punctate epithelial erosions, irregular/hazy corneal epithelium, epithelial defects, subepithelial haze, stromal scarring and ulceration, and corneal perforation.

The dysfunction of corneal innervation that characterizes NK can be due to damage to the trigeminal nerve anywhere along its path from the trigeminal nucleus to the trigeminal ganglion and onto the postganglionic fibers that innervate the cornea. Corneal nerve dysfunction leads to the signs of NK and its progression because corneal nerves and corneal epithelial cells interact with each other in a mutually supportive relationship **(Figure 1)**.[1-4] Corneal nerves act in maintaining corneal epithelial integrity by mediating the protective blink reflex and tear secretion. In addition, the nerves release neuropeptides that provide trophic support for epithelial cells, promoting their proliferation, migration, and adhesion. Corneal epithelial cells serve in supporting the growth, survival, and differentiation of developing and mature neurons through their release of neurotrophic factors, including nerve growth factor.

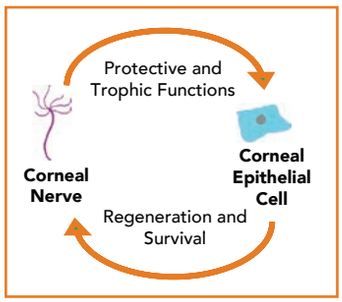

Figure 1. Corneal nerves and corneal epithelial cells interact in a mutually supportive relationship

Etiology

The etiology of NK includes a myriad of conditions that are associated with injury to or dysfunction of the trigeminal nerve **(Table)**.[2,3] The 2 most common etiologies for NK are herpetic keratitis and neurosurgery for trigeminal neuralgia.[3] Diabetes is the most common systemic disease that can cause NK. Other common etiologies include ocular surgery (iatrogenic NK) and medication-induced disease.

Table. Etiologies of Neurotrophic Keratitis[2,3]

Infectious and Noninfectious Keratitis • Herpes simplex keratitis • Herpes zoster keratitis • Acanthamoeba keratitis • Chemical injury • Thermal injury • Contact lenses	**Iatrogenic** • Ocular surgery – Keratoplasty – Corneal refractive surgery – Collagen cross linking – Retinal photocoagulation – Orbital surgery – Surgery affecting trigeminal nerve	**Congenital Diseases** • Familial dysautonomia • Goldenhar-Gorlin syndrome • Congenital corneal hypoesthesia • Möbius syndrome
Systemic Diseases • Diabetes • Multiple sclerosis • Leprosy	**Medication Induced** • Anesthetic abuse • Topical medication toxicity • Chronic use of antipsychotic drugs • Chronic use of antihistamines	**Trigeminal Nerve Palsy** • Traumatic injury • Intracranial and orbital malignancy • Postsurgical palsy • Aneurysm and cerebrovascular accident

Classification Update

The Mackie classification for NK was introduced in 1995 and divides the condition into 3 stages **(Figure 2)**.[3,5,6]

Recently, a new staging system for NK was developed by the Neurotrophic Keratitis Study Group that divides NK into 7 stages (Neurotrophic Keratitis Study Group, unpublished report, 2020).

In contrast to the Mackie system that clusters several distinct and often nonsequential phases of NK into 3 broad categories,[5] the Neurotrophic Keratitis Study Group classification is thought to better reflect the evolution of NK and more precisely classify its signs and symptoms **(Figure 3)** (Neurotrophic Keratitis Study Group, unpublished report, 2020). Most importantly, the new system was created to increase clinician awareness of the early stages of NK and prompt appropriate evaluation with cornea sensation testing to enable early diagnosis and treatment of NK. The new system is also expected to allow for accurate monitoring of progression or recurrence and assessment of therapeutic response.

In creating the new classification system, the Neurotrophic Keratitis Study Group believed that patients who have Neurotrophic Keratitis Study Group stage 1 NK are often asymptomatic, but that early neurotrophic changes are present (Neurotrophic Keratitis Study Group, unpublished report, 2020). The features defining stage 2 NK are usually diagnosed as dry eye disease (DED). Decreased sensation at this stage, however, should alert clinicians to recognize that stromal involvement can develop after chronic epitheliopathy, even in the absence of an epithelial defect. Diagnosis of NK and initiation of appropriate treatment is important for patients with

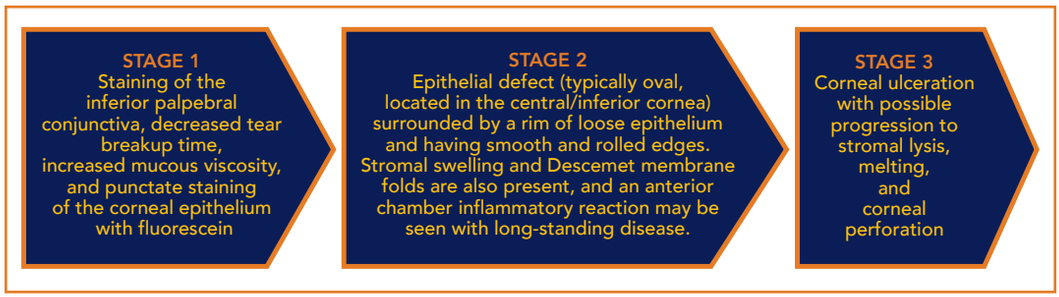

Figure 2. The Mackie classification for neurotrophic keratitis

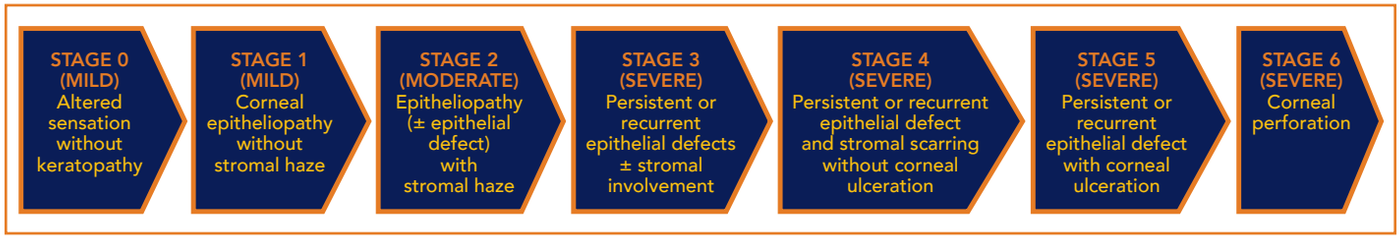

Figure 3. Newly proposed staging system for neurotrophic keratitis by the Neurotrophic Keratitis Study Group

these findings because stromal haze can progress to scarring and loss of vision. Unfortunately, these patients are often misdiagnosed with and mistreated for severe DED.

The features defining Neurotrophic Keratitis Study Group stage 3 NK may lead clinicians to consider a diagnosis of NK and not DED, and thus may prompt corneal sensation testing (Neurotrophic Keratitis Study Group, unpublished report, 2020). Patients with stage 4 NK will have some degree of permanent loss of vision because of stromal scarring, so it is critical to make the diagnosis of NK before it progresses to this stage.

Prevalence and Diagnosis

Francis S. Mah, MD

Publications on NK prevalence and incidence are limited. Authors extrapolating data on the percentage of patients who develop NK in association with its 2 most common causes (herpetic keratitis and postsurgical nerve damage) estimate its incidence at 0.016% (1.6/10,000 persons).[6] A more recent retrospective epidemiologic study calculated that NK has a frequency of 0.11% (11/10,000 persons).[4] With increased effort to identify patients at an earlier disease stage, NK prevalence may be much higher than previously suggested.

Diagnosis of NK has been based on clinical history revealing a condition associated with trigeminal nerve impairment along with the presence of persistent epithelial defects (PEDs) or ulcers and decreased corneal sensation, which is the linchpin for establishing the diagnosis.[6] PEDs and ulcers, however, are late manifestations of NK that are associated with vision loss. Clinicians should maintain suspicion for NK and screen for it by checking corneal sensation in patients who present with early signs—such as no complaints of discomfort, possible complaints of fluctuation in vision despite punctate keratitis, and/or whorl or irregular corneal epithelium—and who are found on history or examination to have a condition associated with trigeminal nerve impairment (eg, diabetes, chronic contact lens wear, chronic DED, penetrating keratoplasty, extraocular motility issues).

Corneal sensation can be assessed qualitatively to determine if sensation is absent or present when touching the cornea with a cotton wisp or other material or by using a device (eg, Cochet-Bonnet esthesiometer, Belmonte gas esthesiometer) that quantifies the degree of hypoesthesia/presence of anesthesia in different sections of the cornea[3] **(See Sidebar – Expert Discussion: Assessing Corneal Sensation in Practice)**. Corneal sensation testing can be performed by technicians and should be done before any anesthetic drops are placed in the eye.

Treatment for Neurotrophic Keratitis

Preeya K. Gupta, MD

The primary goals for treatment of NK are to restore corneal integrity and prevent progression. Treatments for NK are categorized as nonsurgical, surgical, or medical; each of these categories comprises a range of modalities. The therapeutic approach to NK follows a severity-based stepladder approach, uses the available therapies in combination, and incorporates management of any underlying or exacerbating conditions. Only medical therapy with cenegermin (recombinant human nerve growth factor), 0.002%, and surgical intervention using corneal neurotization directly target the nerve pathology underlying NK.[1,3]

Regardless of NK severity, medical management should include ocular surface lubrication and elimination of offending agents.[3,6] All artificial tear products should be preservative free. Benzalkonium chloride–containing topical products and nonsteroidal anti-inflammatory drugs should be avoided. Patients on glaucoma medications should be switched to preservative-free drops or be considered for laser or minimally invasive glaucoma surgery in order to eliminate or reduce the need for medical therapy. Also, any unnecessary topical medications should be discontinued.

Topical antimicrobial therapy can be considered if there is an epithelial defect, and oral antiviral treatment should be initiated for patients known to have herpetic keratitis.[3,7] Patients thought to have inflammatory DED can be checked for inflammation with the matrix metalloproteinase-9 assay; if the test result is positive and

Expert Discussion: Assessing Corneal Sensation in Practice

Dr Mah: The Cochet-Bonnet esthesiometer is an excellent tool for quantitatively measuring corneal sensation, but not all practices have this device; virus transmission is also a concern with its use. The Belmonte gas esthesiometer is a sophisticated, sensitive instrument for assessing corneal sensation that tests reactions to mechanical and thermal stimuli, but is not widely available. How do you test corneal sensation?

Dr Holland: We use a Cochet-Bonnet esthesiometer in clinical trials, for which we need quantitative data, but something simpler is needed for clinical practice. I used to touch the cornea with a wisp formed at the end of a cotton-tipped applicator, but I have since adopted the technique of using the rolled-up end of a piece of tissue.

Dr Gupta: I like to use dental floss because it has a sharp-pointed end, but it should be unwaxed floss without mint or other flavoring. A cotton-tipped applicator and piece of tissue also work. Clinicians should just find something that is easy for them to use.

Dr Mah: When integrating corneal sensation testing into patient evaluations, clinicians need to educate technicians to recognize patients who might require such testing so that they do not instill anesthetic drops before the assessment is done. Such patients include anyone being seen because of a persistent corneal abrasion, epithelial defect, dry eye, fluctuating vision, or foreign body sensation.

Dr Holland: The rule in my clinic is that technicians should not put any drops in the eyes of new cornea patients until after a clinical examination is performed.

Dr Gupta: I also instruct my technicians not to put any drops in the eye of a patient who has a known corneal condition or who is coming in for a dry eye evaluation. Our technicians also like to stain the cornea of such a patient to check for a defect so that they know if it is okay to get an intraocular pressure measurement, but they use a fluorescein strip with a drop of balanced salt solution instead of fluorescein drops that might contain an anesthetic.

Dr Mah: Dr Holland, do you check corneal sensation in all quadrants?

Dr Holland: I do, because the sensation can differ between quadrants, particularly when NK is related to herpes simplex virus or varicella-zoster virus keratitis. For example, a patient may have had an inferior temporal lesion with the viral infection and no corneal sensation in that quadrant but normal sensation elsewhere. I recommend testing in all 4 quadrants or even centrally, plus 4 quadrants.

Dr Mah: I agree. Determining if there is a certain area where the sensation is particularly affected may also help with determining the etiology.

there is no infiltrate, anti-inflammatory treatment can be started with a short tapering course of a topical corticosteroid and cyclosporine or lifitegrast as maintenance therapy.[3] Oral doxycycline also provides anti-inflammatory activity and may be especially useful in patients with concomitant lid margin disease. Other treatments that can be used as medical therapy for NK include autologous serum tears, oral omega-3 supplementation, and topical cenegermin, which is the only medical intervention with a US Food and Drug Administration–approved indication for treating NK.[1,3]

Nonsurgical interventions for NK include amniotic membrane placement (cryopreserved or dehydrated); scleral lenses for patients who suffer from chronic ocular surface breakdown; therapeutic bandage contact lenses (BCLs); nonsurgical eyelid closure using botulinum neurotoxin type A injection or taping; punctal occlusion; and humidification.[3]

Surgical treatments include debridement of rolled edges of an epithelial defect, which can enable epithelial cell migration; tarsorrhaphy, which is used for patients with chronic exposure and resulting epithelial breakdown; conjunctival flaps; glued or sutured amniotic membranes; tissue adhesives to repair perforations; keratoplasty in the setting of an unstable cornea with an impending perforation; and direct neurotization to restore trigeminal nerve function.[3]

Cenegermin

The approval of cenegermin was supported by the results of 2 vehicle-controlled clinical trials, in which patients used their assigned treatment 6 times a day for 8 weeks.[8,9] In both studies, complete corneal healing was achieved by 72% and 65.2% of patients receiving cenegermin and by 33.3% and 16.7% of patients receiving vehicle ($P < .001$, cenegermin vs vehicle in both studies) **(Figure 4)**. A secondary efficacy analysis of change in corneal sensitivity showed a strong trend toward greater improvement with cenegermin than with vehicle, although the difference was not statistically significant. Eye pain, which may be a sign of returning corneal sensation, was the most common adverse event associated with cenegermin, and its incidence was 2-fold greater with cenegermin than with vehicle (16% vs 8%).[10] Other adverse events occurring at a rate of > 2% in the pooled cenegermin groups were ocular hyperemia (7%), increased lacrimation (5%), corneal deposits (4%), and foreign body sensation (3%).

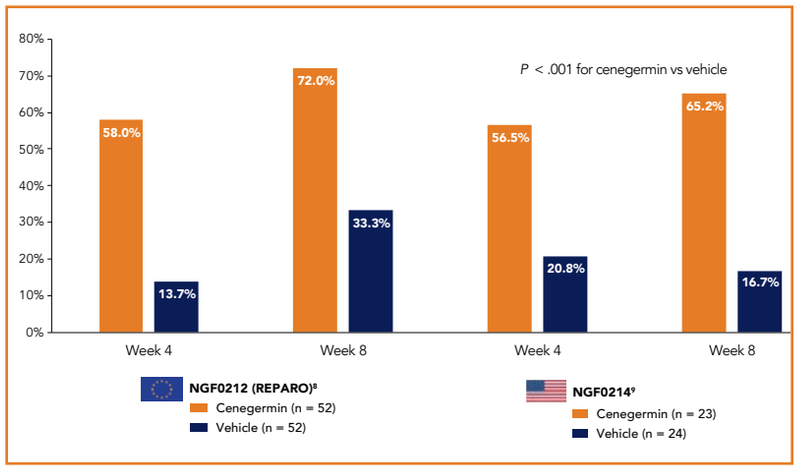

Figure 4. Rates of complete corneal healing (0-mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment) in the cenegermin clinical trials[8,9]

Neurotization

Corneal neurotization addresses the denervation and sensory dysfunction underlying NK, and has been reported to be effective for improving corneal sensation and vision.[11-13] The surgery can be done by direct nerve transfer or via an interpositional nerve graft coapted to a healthy donor nerve. The surgical technique can differ with respect to a number of variables, including incision characteristics, methods of nerve coaptation, instruments and other materials used, number of surgeons required, and surgical duration.[11,13] Although neurotization has generally been reserved for use in eyes with advanced NK, authors of a recent article describing outcomes in a cohort that included patients with Mackie stages 1 to 3 disease reported greater absolute sensory recovery if the surgery was performed earlier in the disease process.[12]

Case Discussions

Case 1: Early-Stage Neurotrophic Keratitis With Lagophthalmos

From the Files of Preeya K. Gupta, MD

A 32-year-old female with a 20-year history of type 1 diabetes presented with DED and exposure keratopathy (OD > OS) associated with incomplete blinking and lagophthalmos that developed 3 months earlier following ptosis repair surgery. She was using artificial tears.

Best-corrected visual acuity (BCVA) was 20/100 OD, corneal sensation was reduced, and there was dense punctate linear corneal staining ***(Figure 5)****.*

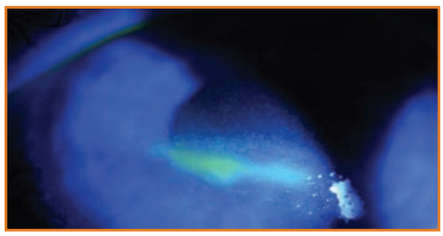

Figure 5. Slitlamp examination image of the patient in Case 1 shows dense punctate linear corneal staining

The patient was diagnosed with Mackie stage 1/Neurotrophic Keratitis Study Group stage 1 NK and treated with a self-retained cryopreserved amniotic membrane. After 7 days, the device was removed and the corneal light reflex was restored, indicating that the corneal epithelium was smooth and intact. Corneal staining was absent. Uncorrected visual acuity (VA) was 20/25. The patient was asked to continue use of ocular lubricants and tape the eyelid at night, and was started on topical cyclosporine.

Dr Gupta: Amniotic membrane can be effective as an acute initial treatment for rehabilitating the corneal epithelium, but it is very important for patients to understand they are at risk for recurrence and need to be maintained on some therapy. How would you have treated this patient?

Dr Mah: Even though she had stage 1 NK, I would want to be somewhat aggressive and would probably also have used the self-retained amniotic membrane, which is available in our office. Serum tears could be helpful, but the preparation takes at least 2 days. I would have also ordered cenegermin and started artificial tears if the patient was not already using them.

Dr Gupta: I also consider cenegermin to treat stage 1 NK, although I generally use it if the patient is not responding to other interventions.

Dr Holland: The important message from this case is that management for NK should not just follow the DED paradigm with the addition of more DED treatments. This patient did well because her management addressed her NK directly and her lagophthalmos. I observe patients when they blink because if the upper lids descend only approximately one-third, I suspect they have nocturnal lagophthalmos.

Dr Gupta: Can you use cenegermin with a self-retaining amniotic membrane?

Dr Mah: Amniotic membranes and therapeutic contact lenses had to be removed when patients were enrolled in the cenegermin clinical trials.[8,9] In practice, I often place a BCL or self-retaining amniotic membrane to manage NK while patients are awaiting delivery of their cenegermin drops. Although I usually remove the device once cenegermin is available, a few patients have used cenegermin with a BCL, and they did not have any problems.

Dr Holland: When I first began to use cenegermin, I would leave a BCL in if a patient had a history of needing the BCL to prevent worsening and if it would be difficult for the patient to return to the office for necessary frequent monitoring. We have found that in many cases, the epithelium can be maintained out of the BCL after initiating cenegermin. If, however, the epithelium breaks down, we resume the BCL for a few weeks and then have another trial out of the BCL.

Case 2: LASIK-Associated Neurotrophic Keratitis

From the Files of Francis S. Mah, MD

A 53-year-old female was referred by a neuro-ophthalmologist for a large central corneal abrasion OD, anesthetic cornea, and decreased vision. She was using topical ciprofloxacin 3 to 4 times a day.

The patient worked at a computer all day. Her history included uncomplicated bilateral LASIK (laser-assisted in situ keratomileusis) in April 2017 and rhizotomy in June 2017 for right-side trigeminal neuralgia that provided no benefit and resulted in right-side face and eye numbness.

The patient reported that her central vision OD became hazier as the day progressed, to the point at which she had to cover that eye to work, and that her vision improved for only seconds after using artificial tears. Clinical findings on examination included an inferior paracentral (oval) epithelial defect with no haze or stromal edema ***(Figure 6)****. Visual acuity was 20/40 OD, with no improvement on pinhole testing, and 20/40 OS, with improvement to 20/20 on pinhole testing.*

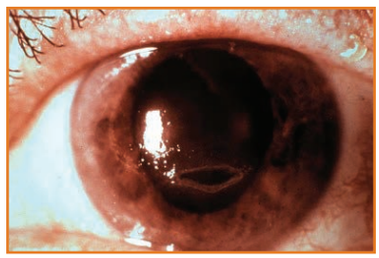

Figure 6. Slitlamp examination image of the patient in Case 2 shows an inferior paracentral (oval) epithelial defect without haze or stromal edema

The patient was diagnosed with Mackie stage 2/Neurotrophic Keratitis Study Group stage 3 NK. Treatment was started with erythromycin ointment OD 4 times a day. Two weeks later, the epithelial defect had healed. The patient disliked the erythromycin ointment because it blurred her vision and would discontinue its use. Over the next year, she developed a recurrence of the

epithelial defect 4 times, but it healed with vision recovery and no scarring when she restarted the erythromycin ointment. She was also treated with a self-retained cryopreserved amniotic membrane and a scleral contact lens that she did not tolerate. Finally, tarsorrhaphy was performed, which was hated by the patient but effective for preventing further breakdown.

In January 2019, cenegermin became available. The tarsorrhaphy was removed in mid-February, and the patient started cenegermin 6 times a day for 8 weeks. The epithelial defect healed by week 4 and remained healed while the patient was maintained on artificial tears. Her VA was 20/25 OD in November 2020.

Dr Mah: Considering cenegermin, amniotic membrane, tarsorrhaphy, and a scleral lens, which do you think would be the least optimal as a long-term solution for this patient who is experiencing frequently recurring epithelial breakdown?

Dr Holland: The risk of scarring increases the longer a defect persists, so I like to use tarsorrhaphy for acute management of an epithelial defect because it is very effective for promoting healing. It would not be a good long-term solution for this relatively young patient, however, because she would likely find it cosmetically unacceptable. In my experience, taping works well for temporary tarsorrhaphy, but patching the eye is not a good option because it does not provide enough pressure to keep the eye closed.

Dr Gupta: I like to do a botulinum neurotoxin type A tarsorrhaphy if I think exposure is a factor in NK, but 3 to 4 days are needed for onset of effect. This involves injecting botulinum neurotoxin type A into the levator to induce ptosis for the duration of the drug effect, which is approximately 3 months. This can be useful for patients who need temporary tarsorrhapy. If there is an active melt, I would keep the patient on artificial tears, place an amniotic membrane, do a botulinum neurotoxin type A or partial lateral tarsorrhaphy, and order cenegermin. Improvement can be seen after just a few weeks on cenegermin, and starting the other interventions provides protection in the meantime.

Dr Mah: I agree that you must use everything available to try to avoid perforation and limit the potential for scarring when there is an ulcer or active melt. I also like to use a cyanoacrylate tissue adhesive for tarsorrhaphy, but one has to be careful that it does not get on the eye. By the time the adhesive breaks down, the tarsorrhaphy is usually no longer needed.

Case 3: Herpes Simplex Virus and Glaucoma

From the Files of Edward J. Holland, MD

A 34-year-old male was seen with Mackie stage 2/Neurotrophic Keratitis Study Group stage 4 NK. He had a 17-year history of recurrent herpes simplex virus epithelial and immune stromal keratitis. At presentation, he had a PED that was present for months with stromal scarring ***(Figure 7)****. Corneal sensation was 0, and VA was 20/400.*

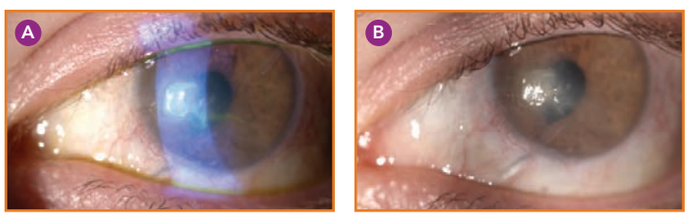

Figure 7. Slitlamp examination images of the patient in Case 3 show a persistent epithelial defect (A) and stromal scarring (B)

The patient had been chronically maintained on antiviral prophylaxis valacyclovir 1000 mg twice daily and was using loteprednol twice daily to control the immune stromal keratitis, but the steroid was stopped whenever his herpes simplex virus keratitis recurred and restarted only when the epithelium healed and the active infection resolved. The patient had chronic glaucoma that was treated with maximum medical therapy and eventually with glaucoma drainage devices placed inferiorly and superiorly. He was using preservative-free artificial tears every 2 hours, and had a permanent BCL to prevent enlargement of the epithelial defect. He was also on serum tears, had punctal plugs, and had been unsuccessfully treated with numerous different amniotic membrane therapies. Tarsorrhaphy was discussed, but declined by the patient. He was told that he would need to return for frequent follow-up visits to check for progression to ulceration.

The patient was started on cenegermin when it became commercially available. After just a few days, he called saying that his glaucoma drops were hurting his eyes. At the end of the 8-week course, the epithelial defect had healed, corneal sensation recovered to 3 out of 4, and VA was 20/100 ***(Figure 8)****. For the first time in 10 years, the patient no longer needed to have a BCL and did not need such frequent follow-up visits.*

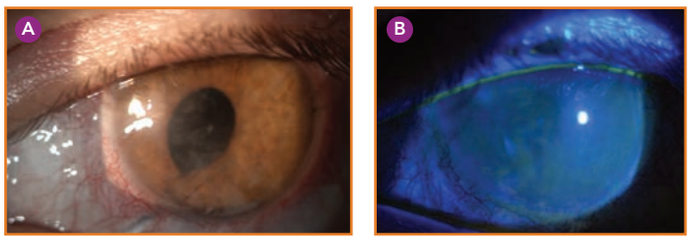

Figure 8. Images of the patient in Case 3 after cenegermin treatment show healed persistent epithelial defect and no requirement for bandage contact lens

Dr Holland: I was eager to treat this patient with cenegermin when it became available. Obviously, the patient wanted better vision, but the immediate goal was to heal the defect, and his absent corneal sensation made him a terrible candidate for a keratoplasty. Treatment with cenegermin was truly life altering for this patient, although keratoplasty is still something to consider in the future.

This patient was one of the first cases I treated with cenegermin, and his response made me understand its clinical benefits. Anecdotally, it is my impression that younger patients respond better than do older patients, and that complaining about discomfort after starting cenegermin is a good sign because it likely indicates that corneal sensation is returning.

How would you treat this patient? Would you insist on tarsorrhaphy, use cenegermin, or recommend penetrating keratoplasty or deep lamellar keratoplasty, considering his deep scar?

Dr Gupta: I think he was a great candidate for cenegermin, and it was a more attractive alternative to the surgical options for this young patient. Its benefit does not guarantee that he will not need surgery in the future, but I expect this patient appreciated not having another operation at the time.

Case 4: Acoustic Neuroma Surgery

From the Files of Preeya K. Gupta, MD

A 70-year-old male who had undergone surgery 10 years earlier for a left-sided acoustic neuroma presented on referral for DED because of limited response to topical lubricants, punctal plugs, serum tears, and an amniotic graft. The patient said that his vision in the left eye had been poor for "a while". He had a posterior chamber intraocular lens from previous cataract surgery. Findings on examination were BCVA 20/400 OS, very reduced corneal sensation (floss test), and diffuse 3-4+ punctate epithelial keratitis ***(Figure 9)****.*

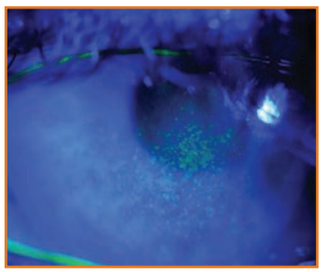

Figure 9. Slitlamp examination image of the patient in Case 4 shows diffuse 3-4+ punctate epithelial keratitis

The patient was diagnosed with Mackie stage 1/Neurotrophic Keratitis Study Group stage 1 NK related to iatrogenic nerve injury. He was started on an 8-week course of cenegermin in early to mid-March. The clinic shut down soon after because of the COVID-19 (coronavirus disease 2019) pandemic, but in a telephone consultation 4 weeks into his treatment course, the patient said he was extremely happy because he was able to see. When seen in the clinic after he completed the cenegermin course, the patient had 20/30 uncorrected VA and 20/25 BCVA, restoration of the corneal light reflex, and no corneal staining. The patient was instructed to continue using topical lubricants, lifitegrast, and an ocular lubricant ointment at night.

Dr Gupta: Acoustic neuroma surgery risks disruption of the trigeminal nerve pathway, so this patient's history and the finding of poor vision on the side where he had the surgery raised suspicion for NK. I think it is reasonable to try a nonprescription therapy for approximately 1 month to treat stage 1 NK if it is not an urgent or emergent situation.

Dr Holland, how do you treat stage 1 NK?

Dr Holland: Most patients I see have already been treated with multiple medications, but I would definitely start a trial of nonprescription therapy for someone with stage 1 NK if it has not been tried.

Dr Gupta: Dr Mah, do you immediately start treatment with a prescription topical medication for somebody who has a concomitant condition, such as limbal stem cell deficiency, or will you start with nonprescription therapy?

Dr Mah: The patients I see have already tried multiple interventions and are coming to me because they have vision problems that limit their daily activities. Once I confirm the diagnosis of NK by establishing hypoesthesia/anesthesia, I have been starting cenegermin right away. Until cenegermin is received, I keep the patient on whatever has worked best or place a self-retained amniotic membrane or BCL.

Take-Home Points

Neurotrophic keratitis is a condition in which dysfunction of corneal innervation results in dysregulation of corneal and/or cellular function.

- The corneal nerve impairment underlying NK has multiple possible etiologies
- Early diagnosis of NK is important in order to limit the risk of vision-threatening disease progression
- Presence of NK should be suspected and corneal sensation testing should be performed in patients with visual complaints or corneal findings consistent with early NK and in those who have an NK risk factor on history
- Treatment of NK should address etiology when possible and follow a stepladder approach according to severity
- Treatment of NK incorporates multiple medical options, nonsurgical interventions, and surgical modalities, all of which promote healing by protecting the eye and/or providing regenerative factors, and should always aim to avoid potentially toxic topical therapies

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1. Neurotrophic keratitis is caused by:
   - A. Corneal nerve sensitization
   - B. Dysfunction of corneal innervation
   - C. Loss of tear film homeostasis
   - D. Elevated levels of neurotrophic mediators

2. What is the most common cause of NK?
   - A. Contact lens wear
   - B. Conventional LASIK
   - C. Diabetes
   - D. Herpetic keratitis

3. It is believed that NK has been underdiagnosed because:
   - A. Corneal sensation testing is not being performed in eyes with early disease
   - B. The Cochet-Bonnet esthesiometer is not widely available in community practices
   - C. In vivo confocal microscopy for documenting loss of corneal innervation is not used routinely
   - D. The workup is too time intensive

4. Stromal involvement in eyes with NK may be seen:
   - A. Only when there is a history of herpetic keratitis
   - B. Only in association with PED
   - C. In the setting of chronic epitheliopathy with or without epithelial defects
   - D. Only when there is a history of LASIK or keratoplasty

5. What should initial treatment of NK at any stage always include?
   - A. Topical steroid
   - B. Cenegermin
   - C. Ocular lubrication
   - D. Amniotic membrane

6. Approval of cenegermin for treating NK was based on results from 2 clinical trials, in which rates of complete corneal healing were approximately ___ and ___, respectively.
   - A. 33%, 50%
   - B. 50%, 65%
   - C. 65%, 72%
   - D. 75%, 90%

7. How is cenegermin administered?
   - A. For 6 weeks on a tapering schedule
   - B. 6 times a day for 8 weeks
   - C. Combined with a BCL or amniotic membrane to facilitate healing
   - D. Until complete healing occurs

8. Which was the most commonly reported adverse event in clinical trials evaluating cenegermin?
   - A. Edema
   - B. Foreign body sensation
   - C. Eye pain
   - D. Tearing

9. A patient who has been using generic topical timolol maleate for 9 years to treat glaucoma presents with Mackie stage 1 NK and meibomian gland dysfunction. What should the initial treatment regimen include?
   - A. Switching to a preservative-free ocular hypotensive medication
   - B. Punctal occlusion
   - C. Amniotic membrane placement
   - D. Tarsorrhaphy

10. A patient with a history of herpetic keratitis is diagnosed with Mackie stage 2 NK when seen on referral. Progression from superficial punctate keratopathy to a frank epithelial defect occurred despite use of a preservative-free ocular lubricant and compliance with oral acyclovir. Which of the following offers the best immediate treatment?
    - A. Botulinum neurotoxin type A tarsorrhaphy
    - B. Self-retained cryopreserved amniotic membrane
    - C. Cenegermin
    - D. Switching the antiviral treatment to topical acyclovir