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ADVANCES IN THE TREATMENT OF NEUROTROPHIC KERATITIS

NEW APPROACHES FOR CORNEAL HEALING

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ACTIVITY DESCRIPTION

The health of the corneal surface depends on a feedback mechanism that involves sensory innervation. This feedback loop can be disrupted by both ocular and systemic conditions that damage trigeminal innervation of the cornea, leading to the corneal condition neurotrophic keratitis, which is characterized by disrupted tearing and progressive corneal damage that does not readily heal. Until very recently, a lack of effective treatments to reinnervate and heal eyes affected by neurotrophic keratitis served to further hamper efforts toward timely diagnosis. Now that an effective treatment is available, clinicians must strive to identify patients who might benefit before the disease progresses to the point of corneal perforation and subsequent loss of visual acuity. The desired results of this activity are to aid clinicians in gaining knowledge and closing practice gaps related to the pathophysiology of neurotrophic keratitis as well as current best practices for screening, diagnosis, and treatment.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the pathophysiologic mechanisms driving neurotrophic keratitis
- Discuss the relationship between corneal innervation and ocular surface healing in neurotrophic keratitis treatment
- Integrate evaluation of corneal sensitivity into assessment of ocular surface disease
- Review clinical trial data for approved neurotrophic keratitis therapy
- Develop evidence-based treatment strategies for patients with neurotrophic keratitis

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INTRODUCTION

Kenneth A. Beckman, MD, FACS

Neurotrophic keratitis (NK) is a rare sight-threatening corneal disease that often presents a treatment challenge. Historically, management has relied on a variety of modalities aimed to protect the cornea, promote healing, and prevent NK progression, which results in corneal melting and perforation. These treatments, however, were sometimes of limited or temporary benefit because they did not address the pathophysiology of NK, which is loss of corneal innervation.

In 2018, the US Food and Drug Administration approved cenegermin (recombinant human nerve growth factor) ophthalmic solution, 0.002%, for the treatment of NK.[1] This topical agent acts through novel mechanisms to facilitate corneal healing, and it is the only modality that is specifically indicated for the treatment of NK.

In this activity, cornea specialists review NK pathophysiology, diagnosis, and treatment, and provide personal insights on these topics through a series of case-based discussions.

PATHOPHYSIOLOGY OF NEUROTROPHIC KERATITIS

Elizabeth Yeu, MD

Neurotrophic keratitis is a degenerative corneal disease, in which damage to the trigeminal nerve (cranial nerve V) results in loss of corneal sensation and breakdown of the corneal epithelium.[2] Corneal healing is also impaired in NK, so superficial corneal damage may progress to a frank epithelial defect and then corneal ulceration, stromal melting, and perforation.

The pathophysiology of NK is understood on the basis of knowledge of trigeminal nerve anatomy and the critical role that corneal innervation plays in maintaining corneal epithelial integrity and a healthy ocular surface. The cornea, lacrimal glands, conjunctiva, and eyelids are all innervated by sensory branches of the ophthalmic division of the trigeminal nerve.[3] The corneal nerves initiate 2 protective reflexes, blinking and tear secretion, in response to adverse stimuli. The nerves also support ocular surface health by releasing a host of trophic neuromediators—including substance P and calcitonin gene-related peptide—that have been shown to promote corneal epithelial cell proliferation, differentiation, migration, and adhesion.[2] The corneal epithelial cells act in a mutually supportive relationship with the corneal nerves through the release of neurotrophic factors that promote neuronal extension and survival. Impairment of corneal innervation leads to loss of corneal protective reflexes and trophic factors, with resultant spontaneous corneal epithelial breakdown, loss of epithelial cell neural support, and decreased ability of the cornea to recover from damage **(Figure 1)**.

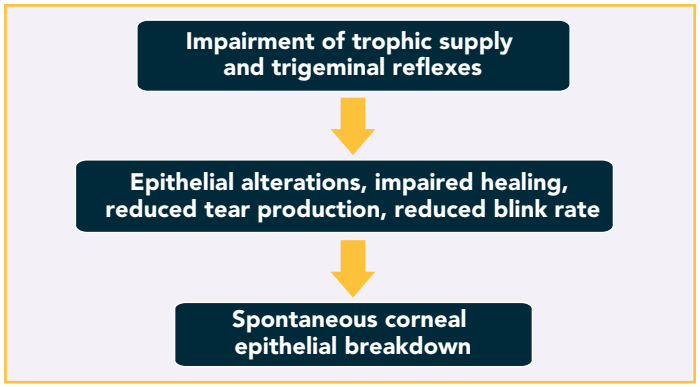

Figure 1. Neurotrophic keratitis is progressive and characterized by the loss of corneal sensory innervation

Nerve growth factor (NGF) is one of the neurotrophic factors released by corneal epithelial cells. Binding to highly specific high-affinity (tropomyosin receptor kinase A) and low-affinity (p75NTR) receptors, NGF supports corneal integrity through multiple mechanisms **(Figure 2)**.[4] NGF stimulates the regeneration and survival of the sensory nerves that innervate the cornea and stimulate tear production and blinking. NGF also binds to receptors on the lacrimal gland to promote sensory-mediated reflex tearing. In addition, NGF acts on the corneal epithelial cells, stimulating cell proliferation, differentiation, and survival, and maintains limbal epithelial cell potential.

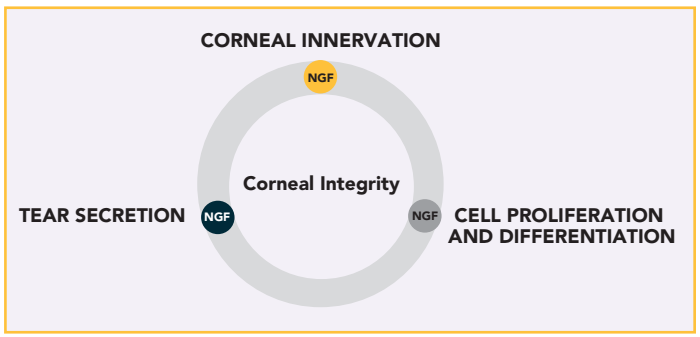

Figure 2. Endogenous nerve growth factor supports corneal integrity through corneal innervation, cell proliferation and differentiation, and tear secretion[4]
Abbreviation: NGF, nerve growth factor.

The etiology of NK includes a large variety of conditions that result in damage to the trigeminal nerve at any level. Two common etiologies underlying NK are herpetic keratitis (herpes simplex or varicella zoster) and neurosurgery for trigeminal neuralgia.[3] Neurotrophic keratitis can also develop in association with systemic conditions—particularly diabetes—and central nervous system diseases; because of chronic dry eye or other causes of ocular surface damage (eg, chronic contact lens wear, chemical/physical trauma, and toxicity from topical drugs or anesthetics); following ocular surgical procedures affecting corneal nerves (eg, cataract surgery, LASIK [laser-assisted in situ keratomileusis], penetrating keratoplasty, and deep anterior lamellar keratoplasty); and with a variety of genetic disorders (Riley-Day syndrome, Goldenhar-Gorlin syndrome, Moebius syndrome, familial corneal hypoesthesia).

STAGING AND DIAGNOSIS OF NEUROTROPHIC KERATITIS

Mark S. Milner, MD, FACS

Staging

A system for classifying NK severity was proposed by Mackie and divides the condition into 3 stages **(Figure 3)**.[3,5,6] Stage 1 (mild) is characterized by punctate epitheliopathy, corneal edema, and haze. Epithelial hyperplasia, superficial neovascularization, and stromal scarring may also be present in eyes with long-standing mild NK.

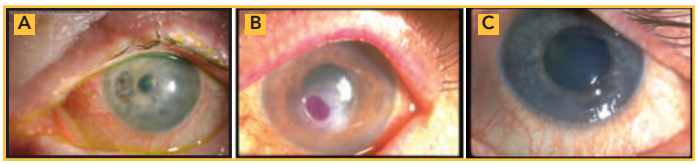

Figure 3. Neurotrophic keratitis is divided into 3 stages defined by the severity of the corneal defect.[3,5,6] Stage 1 (mild) is characterized by superficial punctate keratitis, but there is no epithelial defect (A). A persistent or recurrent epithelial defect defines stage 2 (moderate) (B). In stage 3 (severe), there is a corneal ulcer due to stromal involvement (C).
Figure 3A courtesy of Mark S. Milner, MD. Figures 3B and 3C © 1994 American Academy of Ophthalmology.

A persistent or recurrent corneal epithelial defect with smooth and rolled edges is the hallmark of stage 2 (moderate) NK.[3,5,6] The defect is usually located centrally or inferiorly at the interpalpebral fissure, and is round to oval in shape. Folds in Descemet membrane and stromal swelling will also be seen; with long-standing disease, there can be an inflammatory reaction in the anterior chamber (AC).

The presence of a corneal ulcer with corneal thinning defines stage 3 (severe) NK.[3,5,6] The ulcer can progress to stromal melting and corneal perforation.

Diagnosis

Advanced disease stage portends a poorer outcome for eyes with NK.[7] In addition, successful treatment becomes more challenging with worsening of NK. Therefore, early diagnosis enabling early treatment initiation that can prevent progression is important.

Maintaining clinical suspicion for NK according to awareness of its signs, symptoms, and etiologies is essential for facilitating early diagnosis. Patients with early NK typically present with decreased vision and report ocular dryness.[3] Conjunctival injection tends to be absent, and patients may not complain of pain or significant discomfort because corneal sensation is reduced.

Early signs of NK include tear film instability and other findings related to decreased tear production, inferior conjunctival staining, and corneal staining that is usually central or inferior and shows discordance with symptomatic complaints. A thorough history should be taken to identify a possible etiology for NK (eg, previous surgery involving the cornea, herpetic infection, chemical ocular burns, diabetes, and use of topical medications or anesthetics) that can corroborate diagnostic suspicion and which will be necessary to guide optimal management. The presence of a nonhealing corneal defect, which represents more advanced disease, is a red flag for NK.

Corneal Sensitivity

Establishing the diagnosis of NK hinges on demonstrating reduced corneal sensation. Corneal sensitivity can be tested using esthesiometry, which needs to be done prior to placement of topical anesthetic. The Cochet-Bonnet esthesiometer is a contact device that uses a thin nylon filament to touch the cornea. The filament is gradually retracted from its initial length of 60 mm while force applied on the filament gradually increases. The length at which the patient senses the filament tip is recorded—the shorter the filament length, the lower the corneal sensitivity. Sensitivity is measured in all 4 quadrants of the cornea.

Clinicians who do not have an esthesiometer can test corneal sensation using a cotton tip applicator or a wisp of unwaxed dental floss. The response can be recorded using general descriptive terms (eg, absent, diminished, or present) or with a numerical rating scale (eg, 0 = absence of sensation and reflex, 1 = sensation without reflex, 4 = normal sensation and reflex).

The term neurotrophic keratitis should be differentiated from neuropathic keratitis (also known as corneal neuralgia). Although neurotrophic keratitis has "stain without pain", patients with neuropathic keratitis have "pain without stain" and experience pain in response to minimal or even no stimulus.[8] Neuropathic keratitis can be recognized by asking patients to rate their pain level on a scale of 0 (absent) to 10 (severe) before and after placement of topical anesthesia. A persistent high pain rating when the testing is done with anesthesia suggests neuropathic keratitis.

Differentiation between diseases that lead to NK and those with ocular signs and symptoms that overlap with NK is based on patient complaints of pain and the findings of decreased or absent corneal sensation. For example, keratitis sicca can share features with NK and lead to the disease, but NK is ruled out if the patient maintains corneal sensation. Recurrent erosion syndrome is another consideration, but can be differentiated from NK on the basis of the presence of pain and rapid healing.

Discussion

Dr Beckman: Neurotrophic keratitis is a rare condition, but there is evidence that it is more common than reported.[7] What are your thoughts about why NK may be underdiagnosed?

Dr Yeu: The reasons are probably multifactorial. It may be that the NK is secondary to some other condition, such as dry eye, and when a patient presents with punctate keratopathy or an epithelial defect, clinicians fail to investigate a neurotrophic component or to consider the discordance between signs and symptoms. In addition, clinicians may not even think about NK unless a patient has more severe corneal damage; the previous lack of specific treatments for NK may have also limited efforts to establish the diagnosis.

Dr Beckman: The prevalence of NK may also be higher than previous estimates suggest because patients with early NK may not be bothered enough by their symptoms to seek medical attention.

Dr Milner: I agree with these thoughts. I think the message to clinicians is that they need to start thinking about diagnosing NK in its early stage. This will require consideration of who is at risk and testing corneal sensitivity for patients with superficial keratitis.

TREATMENT OF NEUROTROPHIC KERATITIS

John Sheppard, MD, MMSc, FACS

The corneal epithelium is part of the ocular surface integrated unit, which is composed of 7 components also including the conjunctival epithelium, lids, tarsus, and meibomian glands, lacrimal and accessory secretory glands (the lacrimal functional unit), lacrimal drainage apparatus, cranial nerve V (trigeminal), and cranial nerve VII (facial).[9] This integrated system can be thought of as a 7-piece orchestra that performs only as well as its weakest member. In the case of NK, restoration and maintenance of corneal homeostasis requires correction of trigeminal nerve (corneal nerve) dysfunction and, ideally, its underlying cause.

Treatment of NK aims to restore corneal integrity and to prevent its progression, and should be combined with management of any conditions that underlie or exacerbate the NK, such as dry eye disease.[3] A variety of modalities can be used in the management of NK. Treatment selection usually considers disease severity. Only direct neurotization of the cornea with nerve grafts, amniotic membrane transplantation, and topical NGF have been shown to improve corneal sensitivity.[2,10-12] The recombinant human NGF cenegermin ophthalmic solution, 0.002%, is the only treatment specifically indicated for the treatment of NK.[1] Treatments for NK can be classified as topical, systemic, protective, or surgical **(Table)**.[3,10,13] Eliminating the use of preservative-containing topical agents and minimizing exposure to topical medications that may be toxic to the cornea are fundamental steps for managing all stages of NK.[3] Preservative-free artificial tears are used to protect and lubricate the ocular surface. Topical hypochlorous acid can be useful for lid cleansing in this population because it is nontoxic to the ocular surface and has antiviral, antibacterial, and anti-inflammatory activity.[14]

For systemic therapy, maintenance treatment with an oral antiviral agent should be considered for any patient with a history of herpetic stromal keratitis. Oral macrolides (azithromycin) and tetracyclines provide anti-inflammatory and anticollagenase activity.[15]

Therapies for corneal protection encompass environmental optimization (eg, humidification) along with surgical and nonsurgical interventions.[3] Amniotic membrane placement both protects the cornea and provides a host of trophic and growth factors that activate stem cells and may

Table. Treatments for Neurotrophic Keratitis[3,10,13]

Topical	Systemic	Protective	Surgical
• Preservative-free artificial tears • Steroids • Immunomodulators o Cyclosporine o Lifitegrast • Amniotic cytokine extract • Serum tears • Preservative-free antibiotics • Cenegermin • Intranasal neurostimulation	• Nutritional supplementation • Tetracyclines • Macrolides • Corticosteroids • Antibiotics • Antivirals	• Bandage contact lens • Amniotic membrane • Nonsurgical lid closure o Wound closure tapes o Botulinum toxin o Cyanoacrylate glue • Punctal plugs • Humidification	• Conjunctival flap • Amniotic membrane (sutured) • Punctal cautery occlusion • Keratoplasty • Surface tissue adhesives • Tarsorrhaphy • Direct neurotization

support corneal healing because of their regenerative, anticollagenolytic, anti-inflammatory, antifibrotic, and antimicrobial properties.[16] Tarsorrhaphy is widely used and is effective for promoting corneal healing, but consideration must be given to its adverse functional and cosmetic consequences.[3] Similarly, a therapeutic bandage contact lens (BCL) enables epithelial healing, but also has downsides, including corneal hypoxia and increased risk of infectious keratitis.[17]

The topically applied recombinant NGF cenegermin was recently approved by the US Food and Drug Administration for the treatment of NK on the basis of results of 2 multicenter, double-masked, randomized, vehicle-controlled phase 2 clinical trials showing its benefit for promoting healing of persistent epithelial defects (PEDs).[1,18,19] The REPARO study (NGF0212), which was conducted in Europe, included 109 patients who were treated with vehicle or cenegermin 10 or 20 g/mL and followed for 48 weeks.[18] The US trial NGF0214 compared cenegermin 20 g/mL with vehicle in 48 patients followed for 24 weeks.[19] The formulation of cenegermin used in the US trial contained L-methionine,[19] which is also found as an excipient in the commercially available product.[20] Both studies enrolled patients who had stage 2 or 3 NK.[18,19] The 2 stages were approximately equally represented in the REPARO study, whereas approximately two-thirds of patients in the US trial had stage 2 NK.

In both studies, patients used their assigned treatment 6 times a day for 8 weeks.[18,19] The US study had 2 primary end points: (1) healing of the neurotrophic lesion (PED or corneal ulcer) after 8 weeks, defined as < 0.5 mm of fluorescein staining in the greatest dimension of the lesion area; and (2) corneal healing after 8 weeks, defined as 0 mm of staining in the lesion area and no other persistent staining outside of the lesion area.[19] The primary end point in REPARO was corneal healing, defined as < 0.5 mm of fluorescein staining in the lesion area after 4 and 8 weeks.[18] A post hoc outcomes analysis was also done using the US study's more conservative definition of corneal healing.

For all these end points, cenegermin consistently demonstrated statistical superiority to vehicle.[18,19] Corneal healing at the end of the 8-week treatment period was achieved by 65.2% of 23 patients in the cenegermin group and in 16.7% of 24 patients in the vehicle group in the US study, and by 72% of 52 patients in the cenegermin group and in 33.3% of 52 patients in the control group in REPARO.

The most common adverse event associated with cenegermin was eye pain (16%),[20] which may be interpreted as a sign of nociceptor resensitization.[19] Other common adverse events occurring more frequently in treated patients than in those in the control groups included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and tearing.[18-20]

Discussion

Dr Beckman: A number of systemic treatments have anticollagenase activity. What are the limitations of those treatments? Which topical or systemic treatments that have anticollagenase activity do you like to use?

Dr Sheppard: Tetracyclines and azithromycin have anticollagenase activity and so does N-acetylcysteine, which can be compounded for

topical use.[15,21,22] Identifying and addressing the underlying etiology, however, are critical.

Dr Milner: Compounded sodium citrate drops can be used to reduce collagenase activity.[23] Oral vitamin C may also be helpful for promoting collagen production.[24]

Dr Yeu: Finally, if there is ultimately an epithelial defect, several of our mainstay treatments have been used to close and heal the epithelium. For younger patients and/or those with more advanced disease who are tetracycline sensitive, azithromycin, both topical and oral, can be effective as well.[25]

Dr Sheppard: Whenever indicated, a careful debridement can remove necrotic debris and collagenase from a healing neurotrophic wound.

Dr Milner: In addition, making the diagnosis of NK in an eye with ocular surface inflammation is important because the initial thought is to treat the inflammation with a corticosteroid. Steroids, however, should be used cautiously because they inhibit stromal healing and may therefore lead to corneal melting.[26]

CASE 1

From the Files of Elizabeth Yeu, MD

A 67-year-old female presented in 2018 for worsening vision in her right eye. She reported fluctuating redness and denied pain, but said she occasionally had a mild foreign body sensation. The patient noted that her left eye had been feeling irritated on and off and stated, "Unlike the left eye, I don't feel any irritation in the right eye when wind hits it or if I slice onions."

The patient had a long-standing history of human leukocyte antigen B27 iritis in both eyes that had been controlled with loteprednol etabonate suspension, 0.2%, used once or twice daily. Attempts to withdraw the steroid resulted in flares. The patient noted that recently, she experienced less discomfort when instilling the steroid drop in the right eye.

In 2017, she had an episode of herpes simplex virus (HSV) keratitis in the right eye, and has been compliant with use of valacyclovir 500 mg twice daily. At that time, best-corrected distance visual acuity (VA) was 20/30 OD.

Findings on examination included best-corrected distance visual acuity of 20/70+ OD and 20/25 OS; 1+ telangiectasias on the lower eyelids, worse OD; trace conjunctival/scleral injection OD; diffuse 2-3+ punctate corneal staining with irregular epithelium centrally (1 × 1 mm) but no epithelial defect OD **(Figure 4)**; and 1+ punctate epithelial erosion inferiorly OS. The AC was deep and quiet OU, and the patient had 1+ nuclear sclerotic cataract OU.

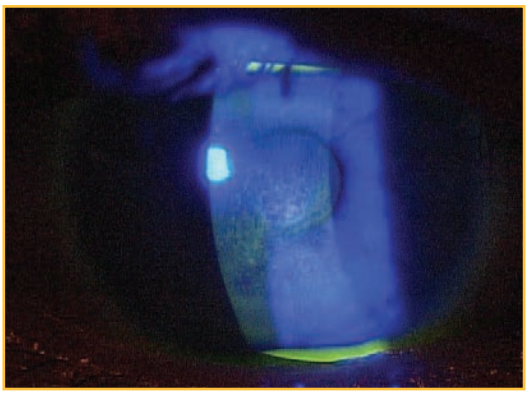

Figure 4. Diffuse corneal staining without epithelial defect in the right eye of the patient in Case 1

Meibography images showed meibomian gland truncation and dropout. The axial curvature topographic map of the right eye showed irregularity, and there was a lot of irregularity of the mires within the central cornea that was consistent with the slit-lamp appearance of the cornea **(Figure 5)**. Corneal sensation testing using a wisp tip of a sterile swab demonstrated no corneal sensation across the right cornea, and healthy corneal sensitivity of the left eye.

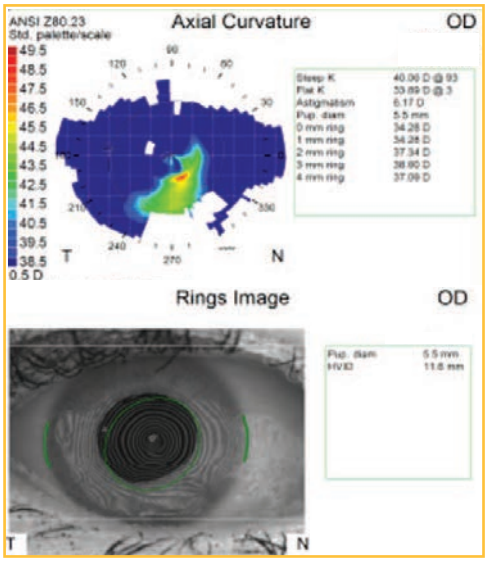

Figure 5. Irregular curvature topographic map and irregular mires of the right eye of the patient in Case 1

Discussion

Dr Yeu: The clinical findings and history for this patient are consistent with a diagnosis of NK. What stage of NK does she have? What first-line treatment would you suggest?

Dr Beckman: According to the Mackie classification, the patient has stage 1 NK because she has epitheliopathy but not a frank epithelial defect.[5] In addition to disease stage, however, I consider duration and response to previous therapy when deciding how aggressive I want to be with treatment.

My concerns in this case are that the underlying HSV infection could be active and that her topical steroid treatment is contributing to the epithelial disease. One approach would be to stop the steroid and see if the epithelium will heal with lubricants, but because her iritis has flared with past attempts to discontinue the steroid, I would switch to a preservative-free steroid to limit corneal epithelial toxicity.

Dr Sheppard: As a uveitis specialist, I am often faced with the need to treat patients with steroid-sparing strategies, and this case is further complicated by the presence of ocular surface disease. One approach is to use a stronger steroid less frequently in order to reduce ocular surface exposure but perhaps without compromising efficacy. I have had some patients with human leukocyte antigen B27 disease controlled using difluprednate just once a week. For a patient who does not have glaucoma, a periocular steroid injection is a consideration. If the uveitis is related to a systemic disease, and especially if the posterior segment is involved, systemic immunosuppression can be used to entirely eliminate the need for topical steroid treatment.

Dr Yeu: I agree that eliminating exposure to topical preservatives could be useful. Loteprednol ointment is the only preservative-free topical corticosteroid that is available commercially. I also wanted to try to optimize the ocular surface by treating the meibomian gland disease (MGD) with mainstay therapies.

Case Continued

Treatment of the right eye was started with compounded preservative-free dexamethasone, 0.025%, once daily and loteprednol ointment, 0.5%, at bedtime twice weekly to reduce the lid margin inflammation. For treatment of MGD, the patient had microblepharoexfoliation and thermal pulsation and was started on oral omega-3 fatty acid supplementation containing gamma linolenic acid.

The patient returned for frequent follow-up visits. After 4 months, improvement was noted on the basis of greater regularity of the mires on the topographic image **(Figure 6)** and reduced epitheliopathy (1-2+), but much greater staining was noted on the right side.

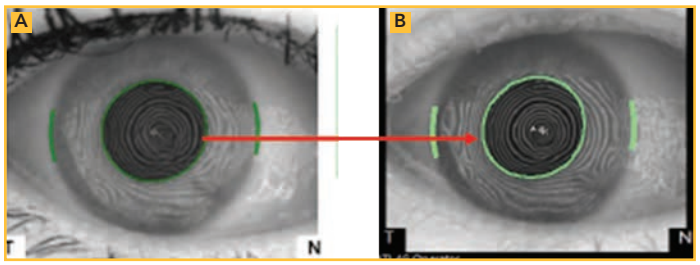

Figure 6. Baseline (A) and follow-up (B) topography images show improvement in the regularity of the mires after 4 months of treatment of neurotrophic keratitis and meibomian gland disease

Discussion

Dr Yeu: What would you do next to treat this patient?

Dr Sheppard: I would use an amniotic membrane. The sutureless product is covered by virtually all insurance companies; in our market, it has been approved on the same day. If that does not work, I would send in an application for cenegermin to the central pharmacy. In Europe, cenegermin is indicated only for the treatment of moderate or severe NK,[27] but the indication in the United States does not specify NK stage.[20] Clinicians might want to consider using cenegermin to treat "bad" stage 1 NK, with the aim of preventing disease progression.

Dr Yeu: When would you consider punctal occlusion for this patient? I always like to quiet ocular surface inflammation before I occlude the puncta so that the ocular surface is not exposed to an elevated concentration of inflammatory mediators in the tear film. I also consider the level of tear production, however, because when it is low, it may be helpful to occlude the puncta to create a more diluted tear film. Because the patient in this case did not have excessive inflammation, I would consider occluding the inferior puncta as a next-level therapy in combination with amniotic membrane placement, either the cryopreserved device or some other form.

CASE 2

From the Files of Mark S. Milner, MD, FACS

A 37-year-old Hispanic female was seen in July 2007 with bilateral eye irritation that was present for 3 years. She was referred by her oncologist who was treating her for acute myeloid leukemia. The patient had undergone a bone marrow transplant and subsequently developed graft-versus-host disease. She had been using serum tears 4 times daily, and had lower punctal plugs placed by another ophthalmologist. She complained of ocular dryness and itching.

On examination, best-corrected visual acuity (BCVA) was 20/50 OD and 20/40 OS. The patient had trace MGD and blepharitis as well as conjunctival scarring (IIb, IIIb[3]), with foreshortening of the fornix and 3 discrete symblepharon. The patient also had early stem cell dysfunction superiorly with neovascularization OU. Schirmer score (without anesthesia) was 4 mm OD and 2 mm OS, and tear breakup time was 8 seconds OD and 4 seconds OS.

The patient was started on topical cyclosporine and compounded vitamin A ointment, and the frequency of serum tears was increased to 6 times a day. The treatments helped some, but as the patient's ocular condition continued to worsen over time, the following treatments were added: topical steroids, additional punctal plugs, amniotic cytokine extract drops, compounded metronidazole ointment, dehydroepiandrosterone drops, tacrolimus drops, and topical albumin. Initially, the patient refused scleral lenses, but she eventually consented, and her vision improved from 20/400 OU with a manifest refraction to 20/70 OD and 20/80 OS. The patient also saw 3 other cornea specialists for additional opinions.

Besides having dysfunctional tear syndrome with severe keratoconjunctivitis sicca, blepharitis, graft-versus-host disease with conjunctival scarring, and stem cell dysfunction, the patient was diagnosed over time with corneal ectasia OU with hydrops OS, Salzmann degeneration, bull's eye maculopathy with a drop in vision from 20/80 to 20/100 OU, retinitis pigmentosa, and cataracts. She wanted cataract surgery and was eventually scheduled for the procedure, although her retina specialist cautioned that it might not result in significant vision improvement. Poor visualization caused cancellation of the cataract surgery, but the patient had the Salzmann degeneration removed.

She maintained her vision for approximately 18 months until she developed acute hydrops OS, which caused her VA to drop to hand motion. The corneal edema and neovascularization improved, but scarring developed and VA remained hand motion.

Options for rehabilitating her left eye vision were discussed, and the patient underwent penetrating keratoplasty with extracapsular cataract extraction and a posterior chamber intraocular lens in June 2019. Postoperatively, she had a complete defect over the graft that healed after 1 month with placement of the cryopreserved amniotic membrane and a contact lens. Five days later, she developed a repeat defect (4 × 7 mm) that was slow to heal. On July 29, 2019, she had a PED that measured 3 to 4 mm; 2 days later, treatment was started with cenegermin 6 times daily OS. After 5 weeks, the PED was reduced to 0.8 × 1.1 mm **(Figure 7)**, but the patient complained of eye pain that did not improve with refrigeration of the cenegermin, and she stopped its use. Her VA was count fingers at 1 foot. She refused tarsorrhaphy and had a self-retained cryopreserved amniotic membrane placed. Approximately 1 week later, the defect had improved but was not resolved, and the amniotic membrane had not yet dissolved. Six days later, the defect had resolved, the amniotic membrane had dissolved, and VA was hand motion OS. On follow-up 10 days later, neovascularization and haze were decreased **(Figure 8)**, the defect remained healed, and VA was 20/400 +1.

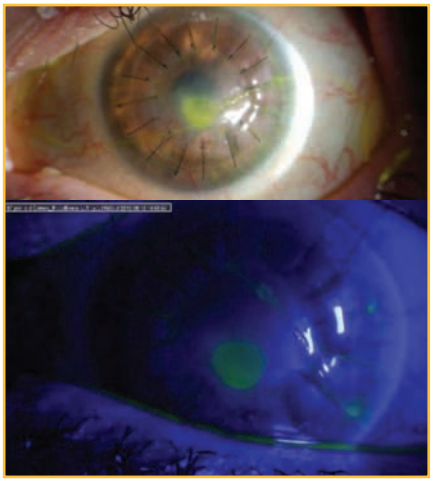

Figure 7. Persistent epithelial defect after keratoplasty in the left eye of the patient in Case 2

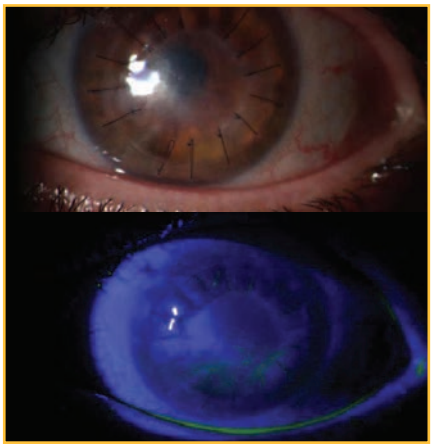

Figure 8. Decrease in neovascularization and haze and corneal healing was seen in the left eye of the patient in Case 2 after a 5-week course of cenegermin and cryopreserved amniotic membrane

Dr Milner: I think the take-home message from this case is that there is no panacea for NK. It is a complex condition that needs multimodal treatment and is best managed by treating the root cause. We have all seen patients whose cornea heals with tarsorrhaphy or a bandage contact lens, but then breaks down when those interventions are

removed. What is needed is treatment to heal the epithelium and restore the health and trophic activity of the corneal nerves to maintain corneal integrity.

In this case, the patient's cornea healed with the first amniotic membrane, but it broke down quickly. It then responded to cenegermin and improved even more when the amniotic membrane was added.

Dr Yeu: Even with cenegermin, which treats the root cause, I think combination treatment is going to be key for expediting corneal re-epithelialization. Keep in mind that once you decide to use cenegermin, it might take time before it gets into the patient's hands. In the meantime, some other treatment should be used to promote healing. A BCL can help with re-epithelialization, but close follow-up is critical because of the risks for infection and NK progression that can go unnoticed by a patient who lacks corneal sensation.

Dr Sheppard: As Dr Yeu mentioned, once the decision is made to use cenegermin, it can take several weeks before it will be available for the patient to start treatment. Because of the delay, I frequently employ cryopreserved amniotic membrane as an induction, or bridge, therapy. The amniotic membrane stays on the eye for approximately 7 days, and provides a variety of regenerative factors for the corneal nerves and other components of the ocular surface integrated unit. In addition to using this combination sequential approach, it is important to simultaneously address any associated diagnoses that caused or are exacerbating the NK.

Dr Beckman: I know that some ophthalmologists are using cenegermin together with amniotic membrane or a BCL, but I have not. I am not aware of any information stating it should not be done. My concern is that those protective devices might limit the bioavailability of cenegermin.

Dr Milner: The amniotic membrane may also act as a reservoir for medications, but we do not know how well cenegermin works when it is present.

Dr Beckman: What do you use for maintenance therapy once the cornea has healed?

Dr Yeu: It depends on the etiology of the NK and its severity. In any case, treatment is selected with the goal of optimizing the ocular surface and regular follow-up.

CASE 3

From the Files of John Sheppard, MD, MMSc, FACS

A 32-year-old Asian female presented with photophobia and blurred vision OD, but said the eye was not painful. She worked in front of a computer monitor all day, and her medical history included type 2 diabetes, which was poorly controlled, HSV infection OD, and bilateral congenital facial edema.

On examination, BCVA was 20/60 OD and 20/25 OS. Corneal sensation OD tested unanesthetized by sterile cotton tip applicator wisp was absent except inferiorly and was normal OS. Intraocular pressure was 20 mm Hg OD and 16 mm Hg OS. Tear film osmolarity was 320 mOsm/L OD and 306 mOsm/L OS. Other findings were 4+ superficial punctate keratitis (SPK) with 3 mm central haze OD **(Figure 9)**, diffuse 3+ SPK OS, and rare cells in the AC OD. She likely had a previous epithelial defect OD, but it was difficult to see because of central stromal opacity. Thus, her first diagnosis was grade 1 NK.

Previous treatment elsewhere included preservative-free artificial tears; 5% sodium chloride drops for epithelial edema; topical cyclosporine; oral doxycycline; nutritional supplementation with oral omega-3 fatty acids and vitamin C; plastic punctal plugs that caused irritation, warranting their removal; and a topical steroid, which led to increased intraocular pressure. The initial therapies were discontinued, and treatment was changed to preservative-free hyaluronic acid drops, valacyclovir 500 mg twice daily, azithromycin 250 mg once daily, loteprednol ointment at bedtime, hypochlorous acid lid scrubs, and collagen inferior punctal plugs. The patient was also counseled to wear sunglasses.

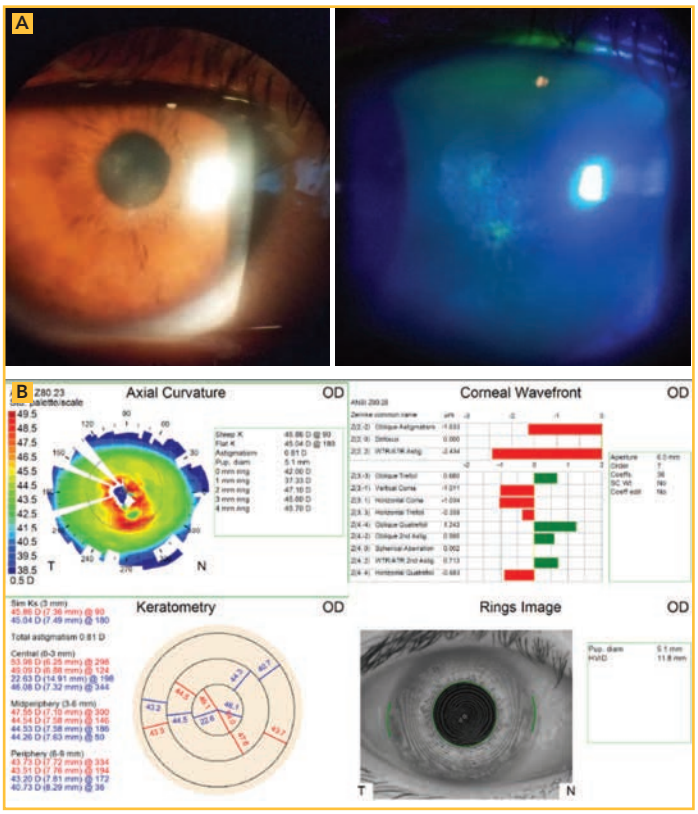

Figure 9. Slit-lamp images of the patient in Case 3 show advanced stage 1 neurotrophic keratitis, with apparent re-epithelialization irregularities and a classic heaped up epithelial healing line (A). Topography was significantly distorted OD (B).

At her next visit after 6 weeks of follow-up, the patient had persistent photophobia, but her BCVA was improved in both eyes (20/50 OD, 20/20 OS). In the right eye, SPK was still 4+, but it was more inferior; the AC was quiet, the stromal haze was improved, but corneal sensation was still absent. SPK in the left eye had improved to 1+. A cryopreserved sutureless amniotic membrane was placed OD.

One week later, SPK improved in the right eye to 3+ and was more inferior, the AC remained quiet, stromal haze was improved, and corneal sensation remained absent. The topographic abnormalities were improved, but corneal higher-order aberrations remained high, contributing to blurring. SPK had cleared in the left eye, and BCVA was unchanged in both eyes. Collagen plugs were placed in the upper puncta, and treatment was started with cenegermin 6 times daily for 8 weeks OD.

When the patient returned after completing the course of cenegermin, BCVA was 20/40 OD and she no longer had photophobia. Intraocular pressure was 16 mm Hg, pachymetry was 504 µm, stromal haze had improved, and corneal staining had improved to 2+ SPK inferior with a clear central cornea. The AC remained quiet.

Treatment was continued with preservative-free hyaluronic acid tears and loteprednol ointment. When the patient next returned 2 months after completing cenegermin, the right eye showed further improvement in BCVA (20/30+), SPK (1+ inferior), stromal haze, topography, and corneal higher-order aberrations **(Figure 10)**.

Dr Sheppard: This patient had stage 1 NK that was related to her diabetes and HSV keratitis. Initial treatment eliminated all potentially toxic topical treatments and resulted in minimal improvement. Amniotic membrane placement resulted in some additional improvement. Treatment with cenegermin resulted in significant resolution that was sustained or even further improved 2 months after she completed this topical biologic agent.

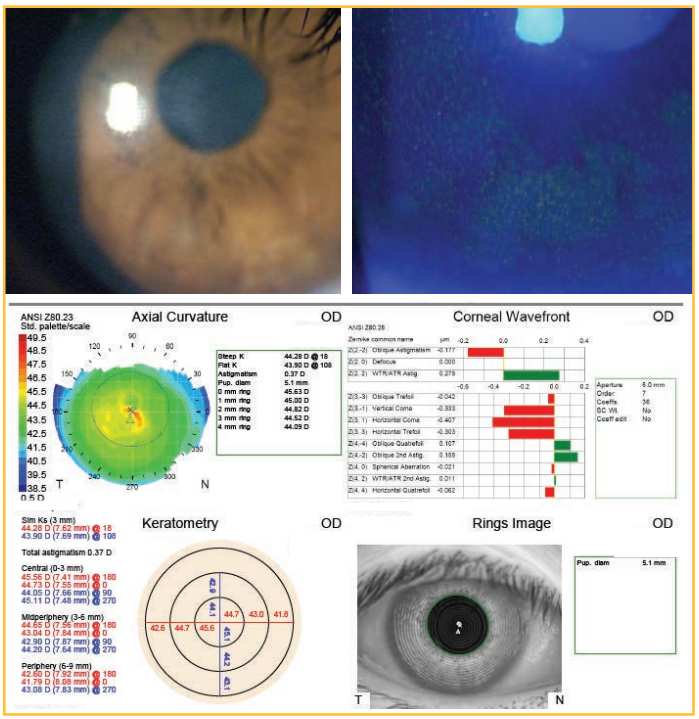

Figure 10. Images of the right eye of the patient in Case 3 two months after cenegermin treatment, showing decreased haze, no central staining, and improved topography

Dr Beckman: A lesson from this case is that we should not wait until NK becomes very severe before considering starting treatment with cenegermin. I believe it is important to consider the duration of the problem and not just the NK stage. If a patient has stage 1 disease with an underlying cause that cannot be eliminated, and if the cornea has not healed with conservative therapy, I think it is reasonable to be more aggressive and to consider cenegermin.

Dr Milner: It was interesting to see in this case that the patient's vision improved from 20/50 when she started cenegermin to 20/40 after completing the 8-week course, but then improved even more at follow-up 2 months later. The progressive improvement is consistent with the idea that nerve regeneration can be an ongoing process after patients are treated with cenegermin.

TAKE-HOME POINTS

Neurotrophic keratitis is a degenerative corneal disease that can be progressive if left untreated and lead to significant morbidity and vision loss.

- The underlying cause of NK is impairment of trigeminal nerve (corneal nerve) innervation, which can occur as a result of multiple possible etiologies

Early diagnosis is key for facilitating effective treatment of this challenging condition.

- Diagnosis of NK begins with clinical suspicion and depends on a careful history and clinical evaluation to rule out other causes for the keratitis and definitively document the loss of corneal sensation

Treatment of NK is based on its severity and its cause.

- Avoidance of potentially toxic topical therapies is integral for treating all stages of NK
- Some therapies promote corneal healing by protecting the eye and/or providing regenerative factors
- Cenegermin is a topical biologic agent that potentially acts via multiple mechanisms to promote healing of PEDs in eyes with NK

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