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NEUROTROPHIC KERATOPATHY: A PRACTICAL APPROACH TO DIAGNOSIS AND MANAGEMENT



Options for treatment and management have improved in recent years.

BY MICAELA CROWLEY, OD

Neurotrophic keratopathy (NK) is a rare degenerative corneal disease with a prevalence of less than five per 10,000 people. It is characterized by lack of sensory innervation and impaired corneal healing. Early stages present with epithelial breakdown, which can lead to persistent epithelial defects and, in severe cases, ulceration, melting, and perforation.¹

Historically, NK was a challenging condition to manage, with limited treatment options. New technologies

and medications have now made it more manageable than ever. This article describes a practical clinical approach to diagnosis and treatment of NK.

ETIOLOGY

Any condition affecting the trigeminal nerve or its branches can result in corneal anesthesia.² The most common cause of NK is herpes simplex or herpes zoster infection. Other causes include chemical burns, refractive surgery, contact lens abuse, chronic use of topical medications,

and surgical procedures for trigeminal neuralgia. Less frequent causes include intracranial masses such as acoustic neuroma.¹ Patients with diabetes have a higher incidence of NK, given their susceptibility to develop neuropathy elsewhere in the body.²

PATIENT PRESENTATION

Given the lack of corneal sensation, patients with NK rarely complain of symptoms. They often present to clinic with blurry vision and photophobia after months of progression.

Photo courtesy of Jacob Lang, OD, FFAAO



Figure. Epithelial breakdown and coalesced superficial punctate keratitis resulting from neurotrophic disease associated with herpes zoster ophthalmicus.

DIAGNOSIS

A thorough case history and slit-lamp examination are pertinent to the diagnosis of NK.³ It is often an arduous diagnosis in its early stages, as corneal signs can mimic other ocular surface diseases (see *Classified Information*). A critical differentiating factor is disproportion of symptoms to corneal signs, where signs exceed symptoms until late stage.

Vital dyes such as sodium fluorescein and lissamine green are helpful in determining epithelial integrity of the

cornea and conjunctiva (Figure). NK is known to be associated with an elevated tear osmolarity and decrease in both tear breakup time and Schirmer test.³ Lacrimal function measurements can provide useful information, although they are not specific for the diagnosis and are often altered in other ocular surface diseases.

The hallmark diagnostic criterion for NK is a decrease in or absence of corneal sensitivity. This can be evaluated in clinic by qualitative and quantitative measures. A qualitative

and easily performed method is the cotton wisp test to determine the presence or absence of sensation in the central and peripheral cornea. Typically, patients with intact corneal sensitivity will respond with a blink reflex or describe the sensation, whereas patients with lack of sensitivity will not be phased.⁴

Quantitative methods are commonly reserved for research and complicated cases. The most popular handheld device is the Cochet-Bonnet esthesiometer (multiple vendors).

Regardless of the method used, testing should always be performed in all four quadrants of the corneal surface, as it is known that the temporal limbus is more sensitive than the inferior limbus.⁵

In vivo confocal microscopy (multiple vendors) is a noninvasive imaging technique that can provide information at the cellular level, specifically cell density, morphology, and imaging of stromal and subbasal nerves. It can be used to compare a patient's corneal cell density and structure to ex vivo histochemical methods. Studies show a significant correlation between decreased subbasal nerve fiber density and corneal anesthesia. In vivo confocal microscopy is exceptional technology, useful in both the diagnosis and management of NK of various etiologies.⁴

MANAGEMENT

Management of NK is based on the severity of the condition. Once the condition is stabilized, it is important to monitor patients regularly to prevent further progression.

Various treatment options can be done at all stages of the condition. When appropriate, all topical medications should be discontinued due to their potentially toxic effects on the corneal surface. When inflammation is nonexistent or minimal, punctal plugs should be considered for retention of tears and their innate healing properties. Preservative-free artificial tears and gels should be generously dosed for regular lubrication of the corneal surface.

AT A GLANCE

- ▶ Neurotrophic keratopathy (NK) is a rare degenerative corneal disease characterized by lack of sensory innervation and impaired corneal healing.
- ▶ NK can be classified into stages based on the severity of corneal damage. Management is based on the severity of the condition.
- ▶ Autologous serum tears, scleral contact lenses, and a recombinant human nerve growth factor are among the treatment options that have shown efficacy against NK.

CLASSIFIED INFORMATION

NK can be classified into three stages based on the severity of corneal damage.⁴

1 STAGE 1: corneal epithelial breakdown. The epithelium often looks dry and cloudy with superficial keratitis and corneal edema. Long-standing disease can present with irregular epithelium due to impaired healing.

2 STAGE 2: recurrent or nonhealing persistent epithelial defects. These are most often ovaloid in shape with rolled edges.

3 STAGE 3: corneal ulcer with stromal involvement. This may be further complicated by stromal melting and perforation.

Scleral contact lenses can be considered a first line of treatment for patients with early or chronic NK. They are an effective nonpharmacologic therapy for corneal healing, providing a protective barrier, preventing evaporation, and delivering constant hydration to the corneal surface.⁶

Challenges can arise in the fitting process due to patients' dexterity issues, small lid apertures, and highly irregular scleral surfaces. Device

stands with LED fixation targets are useful tools to assist with scleral lens insertion. Sophisticated computer-guided design systems such as PROSE (BostonSight) and impression techniques such as EyePrintPro (EyePrint Prosthetics) are available for precise fittings of the most difficult eyes.

Autologous serum tears are loaded with growth factors, immunoglobulins, cytokines, and vitamins that promote proliferation and migration of epithelial cells to maintain homeostasis and healing.³ Studies show that 20% serum tears applied five to 10 times daily can result in corneal healing in 6 to 32 days.⁷ Studies using in vivo confocal microscopy imaging after autologous serum treatment showed increases in mean number, length, width, and density of sub-basal nerves.⁸

Cenegermin-bkbj ophthalmic solution 0.002% (Oxervate, Dompé) is the first FDA-approved medication for the treatment of moderate to severe NK. It is a recombinant human nerve growth factor that is dosed six times a day over an 8-week cycle. In studies, corneal healing was achieved in up to 72% of patients at week 8.^{9,10}

Because cenegermin is a relatively new medication, with FDA approval in August 2018 and the first US patient treated earlier this year, long-term outcomes are not entirely known. However, almost 80% of patients who healed during the 8-week cycle remained healed at 1 year follow-up.⁹ The safety profile is excellent; side effects were localized, mild, and transient. The main complaints were eye pain, increased lacrimation, photophobia, and abnormal sensation in the eye.¹¹

Cenegermin is commercially available for prescription through the specialty pharmacy Accredo. Similar to many eye medications, the prior authorization process can be daunting; however, it has proven worth it for the right patient.

A LESS CHALLENGING CHALLENGE

NK is a challenging condition to manage due to the cornea's inability to heal itself. Until recently, treatment options were limited and did not aim to improve corneal sensitivity; however, improved understanding of the condition and new technologies have made it easier to manage and treat. ■

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