



DOES MY DRY EYE PATIENT HAVE STAGE 1 NEUROTROPHIC KERATITIS?



How to differentiate between the two disease entities.

BY KALEB ABBOTT, OD, MS, FAAO

The corneal nerves originate from the ophthalmic division of the trigeminal nerve via the long ciliary nerves. Until recently, the role of these nerves had largely been overlooked. Now, they may help explain the disconnect between signs and symptoms of dry eye disease (DED). As our understanding of corneal nerves has grown, we have also become aware of nerve-specific conditions, such as

neuropathic eye pain and neurotrophic keratitis (NK).

CORNEAL INNERVATION

The cornea is densely innervated with 7,000 nociceptors per mm^2 , making it 300 to 600 times more sensitive than the skin.^{1,2} Although the cornea's avascular nature allows for a clear structure, it also poses challenges to proper nutritional supply. The corneal nerves play an essential

trophic role in maintaining corneal epithelial proliferation, viability, and overall ocular surface health.^{2,3} Moreover, the corneal nerves are responsible for the motor blink and autonomic reflexes, which stimulate lacrimal gland secretion. These secretions contain nerve growth factor, epidermal growth factor, lactoferrin, fibronectin, vitamin A, lysozymes, immunoglobulins, and albumin, which help maintain ocular

surface health through functions such as cornea epithelial cell differentiation and proliferation.

The degree of sensitivity and function of corneal nerves varies on a spectrum, with neuropathic pain representing one extreme end. In this condition, the nerves are essentially overactive, resulting in misfiring and pain, even in situations where pain shouldn't occur (known as *allodynia*), or when pain sensation is greater than typical (known as *hyperalgesia*). At the other end of the spectrum, there is NK, where poor corneal nerve function leads to an inability to maintain corneal structural integrity and health, yet patients experience disproportionately less symptoms of discomfort than the ocular findings would suggest.

ABOUT NK

NK is an orphan condition with an estimated prevalence of only 16/100,000 patients.⁴ The most common causes of NK are herpetic infection (32.2%, of which the majority are simplex), intracerebral tumors or neurosurgery (27.7%), topical medicamentosa (11%), chronic blepharitis or ocular rosacea (10.7%), and diabetes mellitus (10.5%).⁵ Other risk factors for NK include chronic ocular surface disease, refractive surgery, topical medication use with benzalkonium chloride, chronic contact lens wear, retinal surgery, periorbital surgery, intracranial abnormalities, multiple sclerosis, neoplasms, systemic neurotoxic chemotherapy, epilepsy, and cavernous sinus pathology.⁵ The etiology of NK may stem from corneal nerves, ocular nerves, the trigeminal nerve, the central nervous system, systemic disease, or genetic conditions (Table).

The Mackie Classification method divides NK into three distinct stages based on clinical findings of the cornea and tear film (Figure).⁴ Stage 1 is characterized by punctate keratopathy, reduced blink reflex, reduced lacrimal gland secretion,

TABLE. Etiology Subtypes of NK

ETIOLOGY	CAUSE
Corneal nerves	Herpes simplex Herpes zoster Refractive surgery (eg, LASIK, PRK, cataract surgery) Corneal transplantation Medicamentosa Corneal burns Contact lens wear
Ocular nerves	Retinal surgery Panretinal photocoagulation Cyclophotocoagulation
Trigeminal nerve	Facial trauma Orbital surgery Orbital tumor Ciliary nerve lesion
Central nervous system	Neoplasm (eg, acoustic neuromas, meningiomas) Postsurgical Stroke Aneurysm
Systemic	Diabetes mellitus Multiple sclerosis Leprosy Vitamin A deficiency
Genetic	Riley-Day syndrome Goldenhar-Gorlin syndrome Familial corneal hypoesthesia Moebius syndrome

and potentially an irregular corneal epithelium, anterior stromal haze, or microcystic edema. Progression to stage 2 involves a nonhealing or persistent epithelial defect, which is oftentimes located superiorly due to eyelid friction from poor surface lubrication. Descemet folds or anterior chamber inflammation may also be present. The final stage includes corneal ulceration, stromal lysis, and risk of corneal perforation.⁶

DIFFERENTIATING BETWEEN NK AND DED

Stage 1 symptoms of NK are similar to those of DED. Patients

may describe irritation, foreign body sensation, fluctuating vision, eye pain, or constant blurred vision. However, unlike DED, symptoms of discomfort decrease as severity of NK increases. Patients who have progressed to stage 2 or 3 NK are less likely to report discomfort, but generally report increased symptoms of blurry vision.

Differentiating between DED and stage 1 NK can be challenging because the signs and symptoms are quite similar. Moreover, stage 1 NK is generally accompanied by DED, as the mild corneal nerve dysfunction results in a poor blink rate and reduced tear secretion.

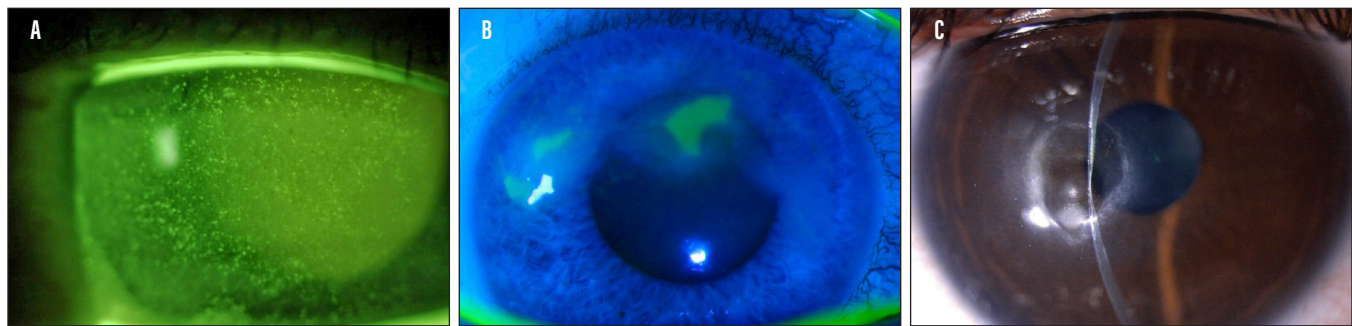


Figure. Mackie Classification of NK. Stage 1 includes punctate keratopathy, decreased lacrimal gland secretion, unstable tear film, microcystic edema, irregular epithelium, and anterior stromal haze (A). Stage 2 includes persistent epithelial defect, Descemet folds, and anterior chamber inflammation (B). Stage 3 includes corneal ulceration with stromal thinning and risk of perforation (C).

The hallmark of NK—and the most straightforward way to differentiate it from DED in its early stages—is the reduction of corneal sensation. Consider testing if traditional therapeutic options for DED have been unsuccessful, or when signs of corneal staining greatly outweigh ocular discomfort symptoms. Testing is also indicated in patients with risk factors for NK, or in cases of punctate epitheliopathy accompanied by an irregular epithelium or mild corneal edema.

Corneal sensation can be clinically assessed using a cotton wisp, dental floss, Cochet-Bonnet esthesiometry, or noncontact esthesiometry (eg, the Belmonte method). Cochet-Bonnet esthesiometry provides quantitative

data on the degree of corneal sensation and is more standardized and repeatable than a cotton wisp or dental floss. Using a cotton wisp or dental floss can be challenging in cases of bilateral NK where the affected eye cannot be compared with a normal eye. Cochet-Bonnet is especially helpful in these cases, as it is possible to know the expected filament length-produced sensation by age.^{7,8} (See *When Should You Consider Stage 1 NK and Corneal Sensation Testing for a Dry Eye Patient?*)

TREATING NK

After diagnosing stage 1 NK, the primary treatment objective should be to prevent progression to stage 2, which increases the risk of infection,

corneal opacification, and vision loss. Although some practitioners suggest a simplistic approach for stage 1 NK, consisting of nonpreserved artificial tears and warm compresses, this treatment is inadequate in resolving punctate keratopathy and does very little to prevent progression, as it does not address the underlying cause of corneal epitheliopathy. Blood-derived treatments such as autologous serum eye drops or platelet-rich plasma can aid in corneal repair and regeneration by providing nutritional support, namely growth factors, which may help in corneal healing and potentially restore corneal nerve function.

Another effective treatment for restoring proper corneal nerve function is cenegermin-bkbj ophthalmic solution 0.002% (Oxervate, Dompé), the only FDA-approved treatment for NK, which is a recombinant human nerve growth factor made from *Escherichia coli* that requires an 8-week course of six drops per day. Amniotic membrane transplantation may also be effective in restoring corneal health. Finally, scleral lenses are an excellent option in stage 1 NK, as they create a fluid reservoir that bathes the cornea during waking hours, protecting it from exposure to the environment.

TAKEAWAYS

In cases of challenging DED where punctate keratopathy is not resolving, it's important to consider

AT A GLANCE

- Differentiating between dry eye disease (DED) and stage 1 neurotrophic keratitis (NK) can be challenging, as the signs and symptoms are similar.
- The hallmark of NK is the reduction of corneal sensation.
- Stage 1 NK is generally accompanied by DED, as the mild corneal nerve dysfunction results in a poor blink rate and reduced tear secretions.
- The primary objective should be to prevent progression to stage 2 NK, where the patient is at increased risk of vision loss and infection.

WHEN SHOULD YOU CONSIDER STAGE 1 NK AND CORNEAL SENSATION TESTING FOR A PATIENT WITH DRY EYE?

CONSIDER TESTING WHEN ONE OR MORE OF THE FOLLOWING STATEMENTS ARE TRUE:

- Traditional therapeutic options for dry eye disease have been unsuccessful;
- Signs (corneal staining) greatly outweigh ocular discomfort symptoms;
- The patient has risk factors for neurotrophic keratitis, such as prior herpetic infection, diabetes, intracerebral tumors or neurosurgery, chronic ocular surface disease, a history of refractive surgery, therapy with multiple glaucoma drops, or trigeminal nerve damage; or
- Punctate epitheliopathy is accompanied by an irregular epithelium or mild corneal edema.

a neurotrophic component and perform esthesiometry (ie, corneal sensation testing), especially if the patient has risk factors for NK or if the ocular surface signs outweigh the symptoms. If a decrease in corneal

sensation is observed, more aggressive treatment options may be needed to nutritionally support the cornea and resolve the corneal epitheliopathy. The primary objective should be to prevent progression to stage 2 NK,

where the patient is at increased risk of vision loss and infection. Whenever possible, focus on treating the underlying cause of disease, rather than choosing a traditional dry eye treatment approach. ■

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