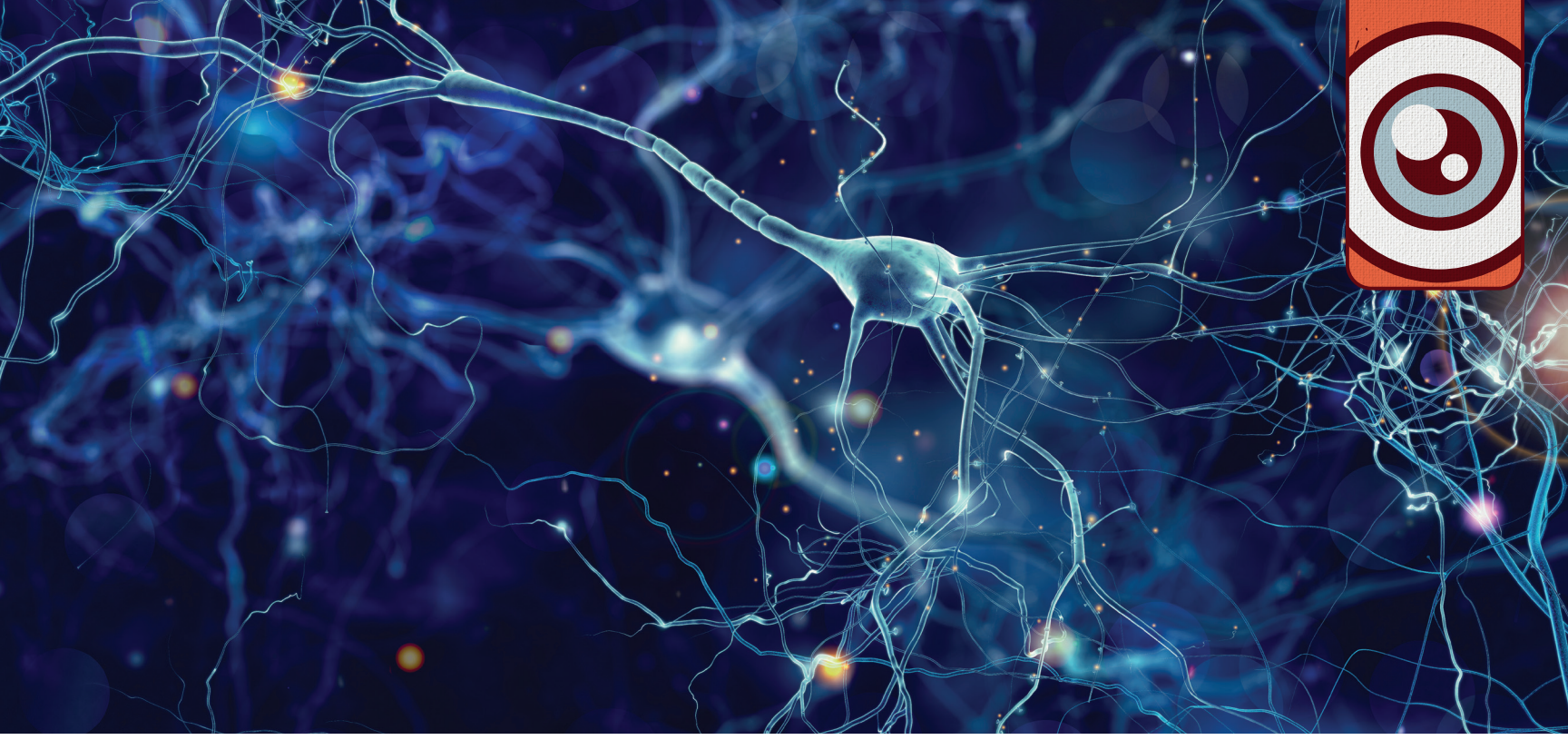

NEUROTROPHIC KERATITIS OR NEUROPATHIC PAIN?

Distinguishing between these two ophthalmic pain conditions based on their causes, symptoms, and treatment.

BY TIM POIRIER, OD

Neurotrophic keratitis (NK) and neuropathic pain may sound similar and can have mutual comorbidities, but they are vastly different when it comes to their causes, symptoms, and treatments. Understanding the differences between these two corneal anomalies and knowing how to manage them can go a long way in providing the care your patients deserve. In this article, I offer a brief distinction between the two.

NEUROTROPHIC KERATITIS

With NK, keep in mind the adage "stain without pain" while evaluating the cornea behind the slit lamp. Clinical examination will reveal significant superficial punctate keratopathy, which can progress to a persistent epithelial defect and ultimately result in a sterile corneal ulcer, stromal thinning, scarring, and/or permanent vision loss. NK is classified into three stages, based on severity (Table 1).[1]

TABLE 1. Mackie Classification of NK

STAGE 1
• Decreased tear breakup time • Punctate epithelial fluorescein staining • Increased mucous viscosity
STAGE 2
• Epithelial defect surrounded by rim of loose epithelium • Edges of defect may become smooth and rolled • Stromal swelling with folds of Descemet membrane
STAGE 3
• Sterile ulcer • Stromal thinning • May lead to perforation

Causes and Symptoms

Numerous etiologies can cause damage to the ophthalmic branch of

TABLE 2. Possible Causes of Damage to the Ophthalmic Branch of the Trigeminal Nerve

OCULAR	SYSTEMIC	CNS	GENETIC
Post herpes infection	Diabetes	Post neurosurgical procedures	Riley-Day syndrome
Ocular surgery	Multiple sclerosis	Stroke	Goldenhar-Gorlin syndrome
Contact lens wear	Vitamin A deficiency	Neoplasm	Mobius syndrome
Drug toxicity	Leprosy	Aneurysm	Familial corneal hypoesthesia
Chemical and physical burns	Amyloidosis	Degenerative CNS disorders	

Abbreviation: CNS, central nervous system

the trigeminal nerve, which leads to NK (Table 2). If the corneal nerves were working properly, NK would produce significant pain similar to that of patients presenting with a corneal abrasion. Symptoms from NK include light sensitivity, difficulty sustaining vision for a prolonged duration, along with decreased vision, stinging, burning, and foreign body sensation. The absence of pain is an important distinction between NK and neuropathic pain, which will be discussed later.

Other comorbidities, such as meibomian gland disease, ocular surface disease, poor noctural lid seal, and contact lens overwear/toxicity to solutions, are often associated with NK, making the diagnosis challenging without a confirmatory test. Corneal sensitivity can be assessed quantitatively with a handheld esthesiometer (Aesthesiometer Cochet-Bonnet 12/100, Luneau Technology), which some tertiary care centers may have. Primary care clinics generally have qualitative tests at their disposal. Alternatively, a practitioner can use dental floss, the teased-out tip of a cotton swab, or the tip of a tissue rolled into a point to test cornea sensitivity. These inexpensive and readily available options will show normal, decreased, or absent corneal sensitivity, confirming NK as the correct diagnosis when corneal sensitivity is decreased or absent. When the tip of a tissue is placed on a normally innervated cornea, the patient will have an immediate blink response.

Management

Historically, NK has been difficult to treat, with main efforts to improve corneal integrity. Topical steroids, autologous serum drops, and amniotic membranes/amniotic drops can help improve the surface of the cornea. The use of cenegermin-bkbj ophthalmic solution 0.002% (Oxervate, Dompé), a topical nerve growth factor medication approved in 2018, allows the nerves to heal as long as other comorbidities are treated correctly. Homeostasis can be restored by getting to the root cause of the disease (ie, poor nerve innervation).

AT A GLANCE

- Neurotrophic keratitis (NK) is a degenerative disease characterized by reduced corneal sensitivity.
- With neuropathic pain, a patient's symptoms are disproportionate to their clinical signs.
- NK has been difficult to treat, with main efforts to improve corneal integrity; for neuropathic pain, a multidisciplinary approach with the collaboration of eye providers, a pain specialist, and a cognitive/behavioral therapist often is needed to improve patients' overall well-being.

NEUROPATHIC PAIN

Our nociceptors can undergo a plasticity process called *peripheral sensitization*, which occurs when nerve injury and inflammatory mediators result in pathologic structural changes of the corneal nerves (Figure). This process lowers the normal pain threshold and causes ectopic discharge of the nociceptors, even with non-noxious stimuli, making the diagnosis of neuropathic pain similar to that of ocular migraine, in that it can feel like a diagnosis of exclusion.

Neuropathic pain, or "pain without stain," occurs when a patient's symptoms are disproportionate to their clinical signs. There may be mild ocular surface disease, possibly

Image courtesy of Scott G. Hauswirth, OD, FAAO

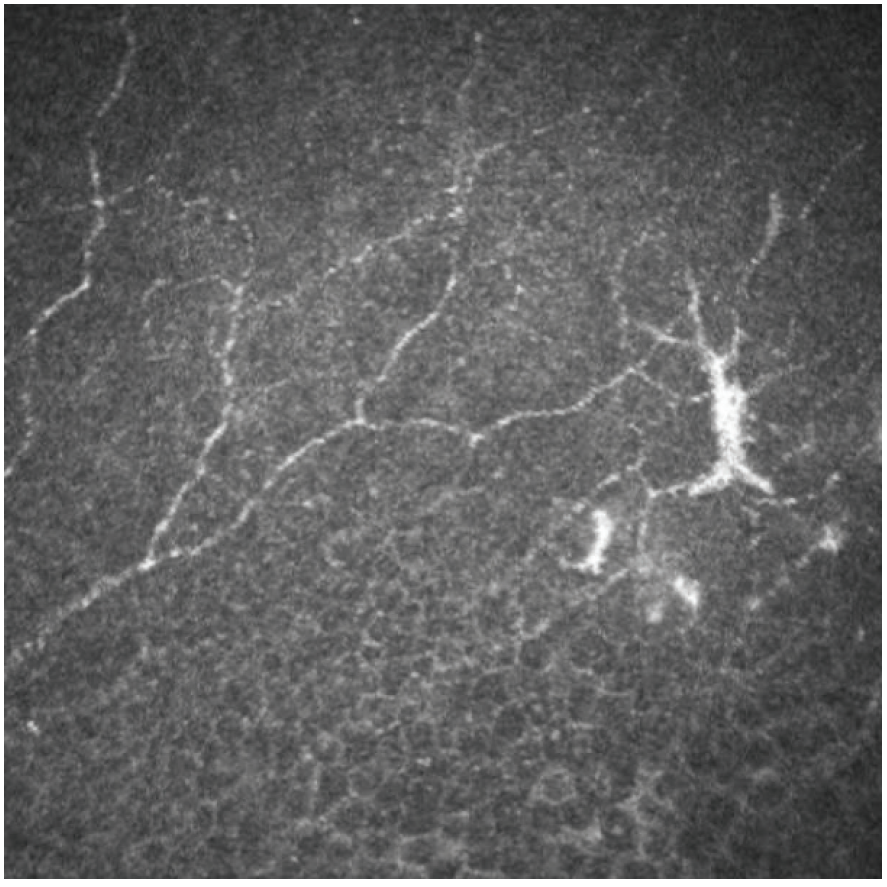

Figure. Microneuromas such as the one shown here (bright spot in image) via in vivo confocal microscopy have been associated with corneal neuropathic disease.

more thickened turbid meibum and minimal superficial punctate keratopathy, but the patient seems to be experiencing significant pain, which doesn't correspond to their clinical picture. Corneal sensitivity testing will produce an increase in discomfort and an excessive reaction when the cotton wisp touches the cornea.

Causes and Symptoms

Etiologies of neuropathic pain include ocular surface disease, toxicity from preservatives, trigeminal neuralgia, infections (eg, herpes keratitis), and radiation keratopathy. Neuropathic pain can also be caused by cataract and refractive surgery.[2,3] Systemic etiologies include diabetes, fibromyalgia and Sjögren syndrome, with anxiety and depression being potentiating comorbidities.

Performing a proparacaine test, which practitioners can do in-office, allows us to decide on treatment options (eg, if the pain is peripheral, then topical medications would be the option; if the pain is central, then treatment would take more of an oral path; if the pain is both peripheral and central, than topical and oral medications can be used). After instillation of one drop of 0.5% proparacaine, the practitioner asks the patient if the pain has resolved, which would indicate a peripheral source; remained the same, indicating a central source; or lessened in severity, indicating a combined peripheral and central source.

Management

Managing neuropathic pain can be challenging and involve a multidisciplinary approach. For peripheral disease, control lid wiper epitheliopathy by making sure the meibomian glands are functioning well. Check for poor lid seal at night and manage inflammation, which can reduce the neuroplasticity of the corneal nerves. Autologous serum contains nerve growth factors, an antiinflammation substance, and can prevent apoptosis in the cornea and conjunctival epithelium. Omega-3 fatty acids and cyclosporine, along with amniotic drops and/or amniotic membranes, can also be helpful.

For patients with more centralized neuropathy, gamma-aminobutyric acid inhibitors, tricyclic antidepressants, and antiepileptic medications can be prescribed. Acupuncture may also have a place as an alternative therapy. A multidisciplinary approach with the collaboration of eye providers, a pain specialist, and a cognitive/behavioral therapist often is needed to improve patients' overall well-being.

KNOWLEDGE IS POWER

Understanding the difference between neuropathic pain and NK can help mitigate a potentially dangerous and difficult-to-treat disease entity and can allow early treatment, which increases the success of restoring homeostasis and ultimately provide a better quality of life for our patients. ■

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