The cornea is the most richly innervated structure in the human body, with 7,000 sensory nociceptors per square millimeter, providing the means to monitor for touch, heat, cold, and noxious stimuli.¹ This innervation provides a wealth of information to the brain, which then responds and makes adjustments to maintain homeostasis of the ocular surface. Homeostasis includes protection and lubrication of the ocular surface via basal and reflex tear secretion as well as the blink reflex.²

When patients describe how their eyes are feeling to us, we assume that those descriptions of sensations of discomfort such as "burning" and "grittiness" are accurate and are caused by actual stimuli proportionate to the level of discomfort. What we are actually assuming is that our patients’ neurosensory systems are functioning normally and that the descriptors they use arise from actual physical stimuli.

However, what if we were to assume that the symptoms our patients were describing were modified in some way, or that they were not caused by physical stimuli? How might that change our approach to managing these patients? Perhaps more important, how would we recognize that this dysfunction exists in any given patient?

WHEN THINGS DON’T ADD UP

It has been a recognized and accepted frustration among clinicians that, in the management of dry eye disease (DED), there is often a discrepancy between symptoms and clinical signs.³ We all likely have seen patients who present with significant symptoms of severe irritation or pain, but upon examination they show minimal if any signs of ocular surface disease. Conversely, it’s also likely that we have been puzzled by patients who present with diffuse corneal epitheliopathy, a sign of severe ocular surface disease, who paradoxically express no complaint of discomfort.

The key to understanding both of these clinical pictures is to account for alterations in function in the neurosensory system. But how does this happen?

DEFINITIONS AND ANATOMY

Neuropathic pain is defined by the International Association for the Study of Pain as “pain initiated or caused by a primary lesion or dysfunction of the nervous system.”⁴ This may arise from injury to the peripheral corneal nerves and nociceptors or from systemic injury or illness.

The most peripheral portion of the neurosensory pathway begins at the nociceptors, which exist in several...
subtypes to detect different stimuli that may cause harm to the tissues of the ocular surface, such as heat, cold, mechanical stimuli, and several types of chemical stimuli. When these nociceptors are triggered, a signal is generated that is then conducted upward through the first-order and second-order neurons and then to the thalamus for the perception of sensation or pain.

If there is injury or inflammation to the ocular surface, however, pro-inflammatory mediators released in the cornea may cause damage to the peripheral axons located therein, leading to a process called peripheral sensitization, which lowers the activation threshold and intensifies the signal. This sensitization causes the patient to have an increased perception of discomfort, even when the stimulus is mild. In addition, because the upward-travelling signal is intensified and our neurologic systems are plastic and can change over time, this increased signal may cause lowering of the thresholds at the synapses between the first and second order neurons, which may eventually lead to pain that occurs independent of what is occurring at the cornea.

Peripheral contributors to peripheral sensitization include DED, ocular surgery, and ocular infection. Systemic conditions that may also contribute include disorders such as fibromyalgia or small-fiber polyneuropathy. Autoimmune diseases such as fibromyalgia create higher amounts of inflammation in the body; the presence of cytokines such as interleukin 1, tumor necrosis factor–alpha, and others increases the chances of the neurologic signal becoming altered at the synapse, leading to amplification of the signal and intensification of symptoms. In addition, comorbid conditions associated with neuropathic pain include anxiety and depression.

**Epidemiology**

There is little real understanding about how frequently neurosensory dysfunction occurs in clinical practice. A first-of-its-kind multicenter study is now under way in an attempt to establish the prevalence of neuropathic pain in patients with dry eye. Begun earlier this year, the Neurosensory Abnormalities in Symptomatic Ocular Surface Patients (NCT04838223) is a single-visit observational study being conducted at 22 locations across the United States, involving both optometry and ophthalmology practices. This study is set up as a challenge test may be used.

**Diagnosis**

Diagnosis of neuropathic pain is challenging. A careful history should be taken to determine if there was an initial triggering event such as surgery or an infection, as well as analysis of symptomology. In many instances, however, identifying neuropathic disease is a process of exclusion. Symptoms may be quantified using validated questionnaires such as the Ocular Surface Disease Index, Standardized Patient Evaluation of Eye Dryness, or Ocular Pain Assessment Survey.

Thorough diagnostic testing should be performed to rule out other sources of discomfort. Examination of the cornea and ocular surface via biomicroscopy and vital dye testing using both sodium fluorescein and lissamine green is recommended. Tear film tests such as tear breakup time, osmolarity, and interferometry are also useful. For example, a very rapid tear breakup time may also trigger signals mimicking chronic burning or pain in an otherwise normal neurosensory system.

If the patient is experiencing intense discomfort and all of these tests are normal, then the proparacaine challenge test may be used. In this test, one drop of 0.5% proparacaine HCl is instilled, and the patient reports to what degree his or her pain is muted. This assists in determining the degree of centralization; any peripheral nociception is nullified. If the patient reports a change in pain level after instillation of proparacaine, from 8 on a scale of 10 to 4 out of 10, then we infer that approximately 50% of the pain may stem from centralized dysfunction.

Another tool available in clinical practice is in vivo confocal microscopy, which allows visualization of the corneal subbasal nerve plexus and may demonstrate nerve morphology changes. The appearance of certain alterations of normal anatomy such as microneurosomas has been associated with corneal neuropathic disease (Figure).
MANAGEMENT

As with diagnosis, management of neuropathic pain is challenging. There has generally been a lack of understanding of this disorder with respect to corneal disease, although this has been changing recently.

Because inflammation seems to be a critical factor for inciting physiologic change in both the peripheral and central portions of the somatosensory nervous system, it must be addressed. Antinflammatory therapy is an essential part of the treatment regimen. Minimizing the ability to generate nociceptive signals may also be helpful, so any therapy that protects the cornea and/or boosts the tear film will likely be a part of the therapeutic plan as well. The latter may include items such as meibomian gland–targeted procedures, scleral lenses, etc.

Neuroregenerative therapies such as autologous serum tears can be quite useful. This is a treatment I employ regularly in this patient group. Patients with contributing systemic disease and other forms of peripheral neuropathy may show improvement with treatments such as alpha lipoic acid or omega-3 fatty acid supplementation.

For patients who have centralized neuropathy and do not respond well to topical proparacaine, systemic medications and alternative therapies may be useful for maintaining improved functionality. These can include gamma-aminobutyric acid inhibitors, tricyclic antidepressants, and antiepileptic medications. Alternative therapies such as acupuncture have been shown to be helpful in patients with chronic pain in meta-analyses.

And finally, in a significant percentage of patients with severe centralized pain, I enlist the help of pain management specialists. These practitioners may opt to perform periorcular nerve blocks using lidocaine and dexamethasone, radiofrequency ablation, or advanced systemic therapies.

An important management aspect to consider is that these patients are suffering, and this is a source for emotional stress and exhaustion. Make sure your patients have the resources and support to access options to maintain their mental well-being. This is not a commonly encountered area in eye care, but it is a crucial one from a longitudinal standpoint. Relief of neuropathic pain increases the prognosis for improving functionality and can be vital for improving the patient’s quality of life.

A CHALLENGING ENTITY

Corneal neuropathic pain is a challenging entity that is often confusing and frustrating for both the patient and the clinician. Knowledge of the etiology and pathologic process of neuropathic pain is growing, as is clinical awareness of this potentially debilitating disorder. We can expect to have increased data regarding its prevalence in the near future. With these changes and increasing awareness, it seems likely that the way we approach patients with “pain without stain” will be much different—and hopefully changed for the better—in coming years.