

CORNEA

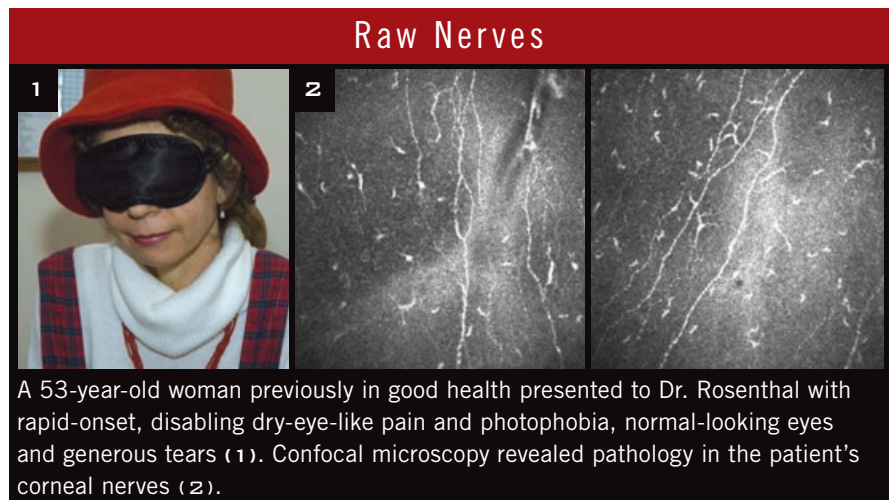
Addressing the Pain of Corneal Neuropathy

BY MIRIAM KARMEL, CONTRIBUTING WRITER

A woman with devastating, unrelenting eye pain and photophobia presented to Perry Rosenthal, MD, after being dismissed by a number of other physicians. First she had seen two different ophthalmologists, who found no supporting signs for her pain and recommended psychiatric treatment. The psychiatrist recommended a pain specialist, who said she suffered from corneal neuralgia and referred her on to a cornea specialist, who, in turn, told her there is no such disease. Finally she found Dr. Rosenthal, who is an assistant professor of ophthalmology at Harvard Medical School and scientific director of the Boston Foundation for Sight. Dr. Rosenthal is on a mission to teach fellow ophthalmologists that such patients may suffer from corneal neuropathic disease. Their pain is real, he said, and it can be excruciating.

The power of corneal pain. The cornea is the most powerful pain generator in the human body, said Dr. Rosenthal. The density of corneal pain receptors has been estimated to be 40 times that of dental pulp. He explained that the damaged nerve fibers in the cornea, the sensory fibers, cause all the symptoms, whether or not the initial disease is severe dry eye or corneal neuropathy.

The intensity and constancy of corneal neuralgia can be incapacitating and even induce thoughts of suicide, said Stephen C. Pflugfelder, MD. Dr. Pflugfelder, who is professor of oph-



A 53-year-old woman previously in good health presented to Dr. Rosenthal with rapid-onset, disabling dry-eye-like pain and photophobia, normal-looking eyes and generous tears (1). Confocal microscopy revealed pathology in the patient's corneal nerves (2).

thalmology and director of the Ocular Surface Center at the Baylor College of Medicine in Houston, had a patient with so much corneal neuropathy following LASIK that he begged to have his eyes enucleated.

Dry eye or neuropathy? Unfortunately, in mild cases, the symptoms, if not the signs, for dry eye and corneal neuropathy can be identical. The same sensitivity to evaporation, wind or dry environments that exacerbates classic dry eye also increases the neuralgia. Patients report severe, unremitting, burning pain and photophobia, Dr. Rosenthal said. Some can't stare at a computer screen without pain.

"Ophthalmologists have never been able to explain satisfactorily why many patients who complain of dry eye symptoms don't have dry eye," said Dr. Rosenthal. "We have been misled by the term dry. Dry eye sensations are nonspecific symptoms of corneal pain.

The question then becomes: "What can cause dry-eye-like pain other than dry eyes?" The only logical answer is corneal hyperalgesia. We've been asking the wrong question and have been targeting the wrong disease. Neuropathy explains it."

Diagnosis

Unexplained corneal pain has confounded cornea experts for decades. And when the pain doesn't respond to dry eye treatment, doctors tend to dismiss the patient, Dr. Rosenthal said. "These patients need special care. These are some of the most devastated patients and they have been marginalized."

Many ophthalmologists are not prepared to identify, let alone treat, corneal neuropathy, in part because they haven't been trained to think beyond objective findings noted on slit-lamp examination. "Ophthalmologists may

not easily diagnose these patients because there is no clinical correlate on exam,” said Pedram Hamrah, MD. “I have seen many patients whose symptoms have been dismissed by physicians. But their symptoms are real. We can actually help these patients and relieve their symptoms.”

Dr. Hamrah, who is assistant professor of ophthalmology at Harvard Medical School and on staff in the corneal and refractive surgery service at the Massachusetts Eye and Ear Infirmary in Boston, became interested in corneal neuropathy when he started seeing exactly those patients who had been dismissed by other doctors. “We began studying corneal nerves in these patients with the *in vivo* confocal microscope, which has a resolution up to 1 μm , and saw nerve abnormalities. In ophthalmology, we are mainly trained to treat what we see. But you can’t see the nerves with a slit lamp.”

Jayne S. Weiss, MD, professor of ophthalmology and pathology at Kresge Eye Institute in Detroit, recalls such a case. A young man presented to her with excruciating corneal pain and evidence of a healed lamellar keratotomy. “Confocal microscopy revealed abnormal collections of unusually tortuous corneal nerves consistent with corneal neuropathy. Although vision eventually recovered to 20/20, the patient had asked at one point if he could have retrobulbar alcohol injected to dull the pain,” she said.

Dr. Weiss cautioned that while some patients with severe pain have indeed been wrongly dismissed, no one has quantified how often this happens. “I think corneal neuropathy exists, but it is not well-defined, and we must be careful to not to think that every patient with pain and a normal slit-lamp exam has neuropathy. I consider the neuropathy diagnosis as requiring unusual pain, a normal-looking cornea plus abnormal confocal findings.”

Treatment

Dr. Hamrah recommended treating the pain of corneal neuropathy palliatively and then sending the patient to a cornea specialist at a tertiary referral

Checklist: Dry Eye or Neuropathy?

CLASSIC DRY EYE. Patients with dry eye have irritation symptoms, such as foreign body sensations, burning and reflex tearing. On slit-lamp examination, the tear film may appear unstable or there may be decreased tear meniscus. In more severe dry eye, there may be fluorescein staining of the cornea and dye staining of the conjunctiva.

TEAR DYSFUNCTION WITH EXCESSIVE SYMPTOMS. Be suspicious of neuropathy when the presentation seems to be classic dry eye but the symptoms are way out of proportion to the dry eye presentation, Dr. Pflugfelder said. It’s still worth treating it as classic dry eye to reduce the pain, and about half of all patients respond to the point that symptoms are tolerable. For the nonresponders, however, neuralgia has to be addressed, he said.

CORNEAL NEUROPATHY. “Whenever you see a patient with dry-eye-like symptoms without equivalent signs, assume that is corneal neuropathy until proven otherwise,” Dr. Rosenthal said. “Corneal neuropathy is a disease in its own right regardless of tear metrics.” Triggers include an episode of zoster keratitis, diabetic neuropathy, chemotherapy, Guillain-Barré syndrome, isotretinoin (Accutane) treatments, recurrent corneal erosions and exposure to noxious fumes or radiation.

center who can perform scanning laser confocal microscopy and treat the underlying condition. Dr. Pflugfelder agreed: If the patient does not respond to the standard dry eye treatments, then the physician must look for other causes of pain, he said. That means looking for nerve abnormalities, either in loss of density or increased tortuosity, or branching with laser scanning confocal microscopy.

Try improving everyone’s tears.

Whatever the etiology—dry eye or neuralgia—Dr. Hamrah recommends starting with artificial tears. When those are ineffective, the fluid reservoir of a nonfenestrated scleral lens can insulate the corneal surface from the stimuli of a hostile environment, Dr. Rosenthal said. The Boston Ocular Surface Prosthesis (formerly the Boston Scleral Lens), developed by Dr. Rosenthal, is a fluid-ventilated gas-permeable contact lens that rests entirely on the sclera, creating a fluid-filled space over the diseased cornea. The lens covers the entire corneal surface, bathing it in fluid, and may provide relief for the neuropathy.

Then treat beyond the symptoms.

For patients who do have neuropathy, treatments that increase the tear layer are palliative at best and don’t get at the underlying disease, Dr. Rosenthal said. After hydration of these severe

dry eyes over a period of days, their surfaces can heal and look perfectly normal, but the patient still may complain of dry eye symptoms, suggesting the presence of neuropathy.

Dr. Rosenthal believes the persistence of pain in the presence of a liquid bandage suggests that dysfunctional pain-generating sites are discharging spontaneously. In these cases, treatment must directly target the dysfunctional corneal nerve terminals and ectopic firing sites. In the past he has had success treating these patients with dilute, sub-hypoesthetic concentrations of local anesthetics in the fluid reservoir of the scleral lens. But more recently Dr. Rosenthal has used the new antiepileptic drug lacosamide. It has the ability, he said, to modulate overactive pain firing sites even though it has no anesthetic properties, adding credence to the notion that the pain is neuropathic. Dr. Rosenthal acquires lacosamide as a topical preparation compounded by Leiter’s Pharmacy and Compounding Center (San Jose, Calif.). “When used as 1 percent eye-drops—the basic concentration used for IV use—it’s effectiveness lasts only 15 to 45 minutes, whereas that same concentration used in the fluid reservoir of our scleral lens can last as long as the patients’ waking hours.”

Unfortunately, some patients are

resistant to lacosamide, perhaps due to maladaptive plasticity in the pain signaling pathway, Dr. Rosenthal said. In these cases, treating the cornea alone is insufficient since much of the pain originates in the trigeminal ganglion and brain, making it a form of phantom pain. Treatment might warrant other systemic anticonvulsants, like gabapentin, pregabalin or carbamazepine. But their effectiveness can be sporadic.

Dr. Pflugfelder agreed. Gabapentin and similar drugs may be used to blunt sensory nerve stimulation or the perception of nerve stimulation, but it doesn't always work and it has side effects. "Unfortunately, I don't think any of us have a good treatment," he said.

"A small percent of patients develop this problem post-LASIK. If a patient presents with chronic pain following LASIK without signs of tear dysfunction, confocal microscopy may reveal evidence of abnormal nerve regeneration. Some patients with this may respond to autologous plasma drops to stimulate nerve repair or the Boston Ocular Surface Prosthesis," Dr. Pflugfelder said.

In the meantime, Dr. Rosenthal has been trying to reverse maladaptive brain plasticity with Scrambler Therapy (Delta). This uses transdermal transmission of encoded electrical signals that are interpreted in the brain as "no pain." The treatment works dramatically in some patients; in others not at all, he said.

What Ophthalmologists Can Do Now






"Doctors should understand it's a problem," Dr. Pflugfelder said. "You should not write these patients off as being hysterical. If they don't respond to the standard dry eye treatment, refer them to a cornea specialist, but one who has familiarity with this problem."

None of the physicians interviewed report financial interests related to the story. Dr. Rosenthal is the founder and an employee of the nonprofit Boston Foundation for Sight but has no financial interest in the Boston Ocular Surface Prosthesis.

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