

Oculofacial Pain: Corneal Nerve Damage Leading to Pain Beyond the Eye

Perry Rosenthal,¹ David Borsook,^{2,3} and Eric A. Moulton^{2,3}

¹Boston EyePain Foundation, Chestnut Hill, Massachusetts, United States

²Center for Pain and the Brain, Boston Children's Hospital, Massachusetts General Hospital, McLean Hospital, Harvard Medical School, Boston, Massachusetts, United States

³Department of Anesthesia, Critical Care and Pain Medicine, Boston Children's Hospital, Boston Massachusetts, United States

Correspondence: Perry Rosenthal, Boston Eye Foundation, c/o 629 Hammond Street, Suite 205E, Chestnut Hill, MA 02467, USA; prosenthal@bostoneyepain.org.

PR, DB, and EAM contributed equally to the work presented here and should therefore be regarded as equivalent authors.

Submitted: August 18, 2016

Accepted: August 31, 2016

Citation: Rosenthal P, Borsook D, Moulton EA. Oculofacial pain: corneal nerve damage leading to pain beyond the eye. *Invest Ophthalmol Vis Sci*. 2016;57:5285-5287. DOI:10.1167/iivs.16-20557

The cornea is supplied principally by the ophthalmic branch of the trigeminal nerve and is the most densely innervated organ in the human body. Under normal conditions, the corneal nerve terminals incorporate sensors that monitor the thickness and integrity of the tear film, which are essential for meaningful vision. A disrupted tear film or direct noxious stimulation of these corneal nerves can produce discomfort or pain limited to the affected surface. Damage to these nerves can sometimes lead to a chronic neuropathic condition, where pain persists months following the initial insult, long after the nerves appear to have healed in the cornea itself following treatment. Neuropathic pain appears to persist indefinitely in a few patients.

Keywords: neuropathic, keratomileusis, CNS, migraine, dry eye, referred pain

Recent studies suggest that many cases of dry eye (DE) have evidence of neuropathic pain that arises from chronic disorders of, as well as acute damage to, the corneal nerves.¹⁻⁵ Dry eye symptoms such as burning, dryness, foreign body sensations, and decreased vision have been reported following ocular surgical procedures that involve the cornea. These include photorefractive keratectomy, laser in situ keratomileusis,⁶ corneal cross-linking for keratoconus,⁷ cataract surgery,⁸ lamellar keratoplasty,⁹ and others. Though these symptoms are typically transient, the chronic symptoms are severe and debilitating in some patients who report classic characteristics of neuropathic pain, including persistent and severe allodynia, hyperalgesia, and dysaesthesia,³ similar to postoperative non-ocular surgical procedures.¹⁰

These sensations can extend beyond the cornea. We have observed patients whose eye pain is accompanied by pain in other areas of the receptive fields of the trigeminal nerve, including the orbits, head, ears, face, jaw, and teeth.⁴ Furthermore, they report painful photophobia that in some patients represents the dominant disabling symptom. Here, we make the case for oculofacial pain as a trigeminal pain that shares many features with the orofacial pain spectrum. Just as orofacial pain is by definition pain felt in the oral cavity and face, oculofacial pain would similarly be defined as pain experienced in the eyes and orbits primarily but may extend to the rest of the face.

As a model of oculofacial pain, consider the often comorbid conditions of DE and migraine/headache.¹¹ Headache and DE share certain pathophysiological features within the trigeminal system. Moreover, sensory changes are multidimensional and can include photophobia. This model suggests how chronic corneal pain may contribute to increased severity of other

components of oculofacial pain. For example, the neuropathic processes underlying DE can lead to increased afferent inputs to the trigeminal system, including neurons in the trigeminal ganglion, second-order neurons in the trigeminal brainstem, and third-order neurons in the thalamus. Such changes can provide a barrage of activity in neurons already affected by the sensory processes of trigeminovascular activation in migraine.¹²

Similarly, changes in corneal nerve morphology have been associated with more severe photophobia in patients without migraine.¹³ Studies in animals have shown that bright light can enhance trigeminal reflex blinks and induce trigeminal sensitization.^{14,15} In a patient with photophobia, multiple levels of the trigeminal pathways were shown to be sensitized to light.¹⁶ The representation of the cornea within the primary somatosensory cortex¹⁷ and other brain regions may provide a basis for the central sensitization of pain. These initial localized changes may induce central sensitization across multiple brain structures, thereby resulting in chronic pain, and ultimately recruiting sensory and emotional areas. Primary damage to corneal nerve endings may exacerbate preexisting underlying diseases (e.g., migraine). Alternatively, while these changes are considered a primary manifestation of a disease, they may also contribute to other painful manifestations in the orofacial region.

Referred pain experienced in regions other than its primary source is a well-described phenomenon in somatic pain,¹⁸ and orofacial referred pain has been described with odontogenic pains.¹⁹ Trigeminal traumatic neuropathic pain following nerve damage from oral surgery has been correlated with abnormal corneal reflexes,¹⁸ suggesting complex interactions across multiple levels of the trigeminal system. Similarly, photophobia



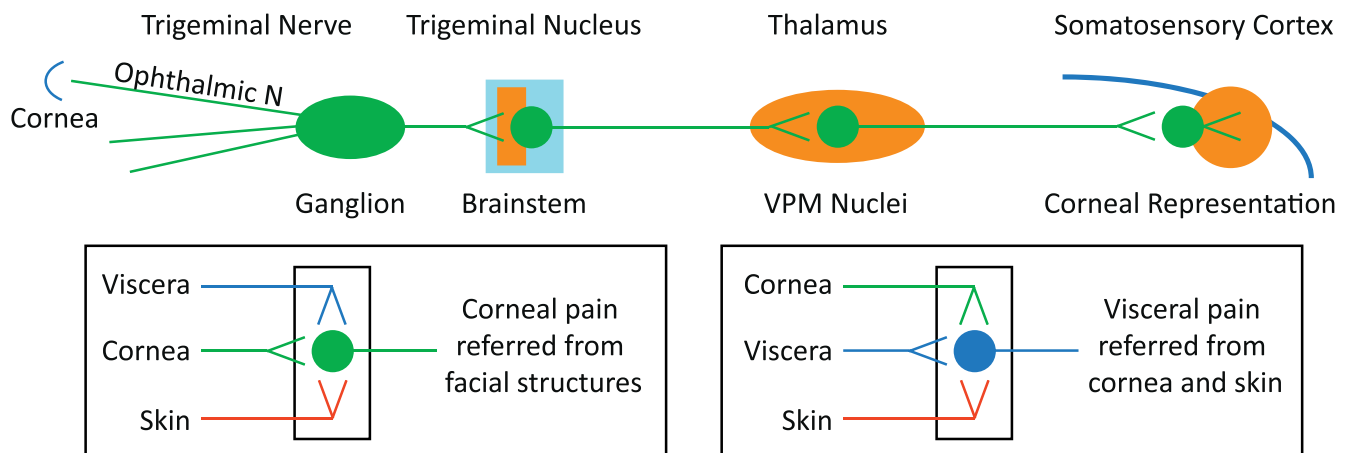


FIGURE. Trigeminal convergence pathway for oculofacial pain. Temperature, mechanosensitive, and polymodal nociceptors transduce noxious input from acute injury or inflammation into neural signals.²⁹ Innervation of the cornea supplies afferents through branches of the ophthalmic division of the trigeminal nerve. These first-order neurons converge with afferent inputs from the other two divisions of the trigeminal nerve (maxillary and mandibular) and are somatotopically organized within the trigeminal ganglion. The neuronal bodies of the trigeminal nerve, located in the ganglion, have central projections that synapse in the trigeminal nucleus. Second-order neurons cross over in their ascending pathway (trigeminothalamic tract) to nuclei within the thalamus (e.g., ventroposteriomedial thalamus). From here, third-order neurons project to the primary somatosensory cortex where the cornea is functionally represented. The boxes below show referred pain (*left*) to the cornea from orofacial somatic and visceral structures and (*right*) to orofacial viscera from the cornea and skin. Such convergence may occur within the central nervous system, potentially involving the trigeminal nucleus and/or thalamus.

is also increased in migraineurs during experimental thermal or painful stimulation of skin.²⁰

The mechanisms underlying referred pain include alterations in central nervous system regions such as the trigeminal nucleus²¹ and thalamus.²² In a rat model with unilateral nerve damage, uninjured nerves may contribute to altered patterns of pain inside and outside of the affected territories.²⁵ In human studies using a capsaicin model, cross-innervated territories develop mechanical allodynia through the process of central sensitization.²⁴ The convergence of neurons that innervate all the trigeminal nerve territories to the trigeminal nucleus is a basis for referred pain (Fig.).^{25,26} How do these observations affect the presentation of oculofacial pain? Previous reports have defined what may be referred pain from corneal structures that have been labeled as “factious disease.”²⁷ The reverse is also worth noting: Corneal pain is diminished in cluster headache,²⁸ presumably through descending inhibitory controls.

We propose the existence of an overlooked trigeminal pain that we have named “oculofacial pain” and suggest that it represents referred pain, perhaps arising from a malfunctioning trigeminal brainstem.²⁸ In our opinion, patients with very symptomatic DE may suffer from a highly disabling pain disease that had been underappreciated because of its characteristic and deceptive lack of appropriate causal signs. On the other hand, some DE patients with significant corneal epithelial disease have few if any symptoms, perhaps due to degeneration of corneal nociceptors. We further argue that because of the severity of symptoms and misleadingly benign appearance of these eyes, the manifestations of this disease have been overlooked in the clinic. Focused efforts to further define oculofacial pain would increase awareness of this disease and improve efforts to understand its underlying mechanisms, which could lead to the development of effective treatments.

Acknowledgments

Supported by the National Institutes of Health, Bethesda, Maryland, United States (Grants 5K24NS064050-09, 4R01NS075018-05, 5R01NS073997-06, 5R01NS095655-02 [DB] and Grant 5R21CA185870-02 [EAM]) and by funding from the

Migraine Research Foundation (New York, NY, USA), the Mayday Foundation (New York, NY, USA), and the Boston EyePain Foundation (Boston, MA, USA).

Disclosure: **P. Rosenthal**, None; **D. Borsook**, Oxford University Press (R), Biogen Idec (C); **E.A. Moulton**, None

References

- Kalangara JP, Galor A, Levitt RC, Felix ER, Alegret R, Sarantopoulos CD. Burning eye syndrome: do neuropathic pain mechanisms underlie chronic dry eye? *Pain Med.* 2016; 17:746–755.
- Galor A, Levitt RC, Felix ER, Martin ER, Sarantopoulos CD. Neuropathic ocular pain: an important yet undervalued feature of dry eye. *Eye (Lond).* 2015;29:301–312.
- Galor A, Zlotcavitch L, Walter SD, et al. Dry eye symptom severity and persistence are associated with symptoms of neuropathic pain. *Br J Ophthalmol.* 2015;99:665–668.
- Rosenthal P, Borsook D. Ocular neuropathic pain. *Br J Ophthalmol.* 2016;100:128–134.
- Rosenthal P, Borsook D. The corneal pain system. Part I: the missing piece of the dry eye puzzle. *Ocul Surf.* 2012;10:2–14.
- Bower KS, Sia RK, Ryan DS, Mines MJ, Dartt DA. Chronic dry eye in photorefractive keratectomy and laser in situ keratomileusis: manifestations, incidence, and predictive factors. *J Cataract Refract Surg.* 2015;41:2624–2634.
- Taner S, Oehler S, Asimellis G, Kanellopoulos AJ. Influence of corneal cross-linking for keratoconus on several objective parameters of dry eye. *J Refract Surg.* 2013;29:612–616.
- Han KE, Yoon SC, Ahn JM, et al. Evaluation of dry eye and meibomian gland dysfunction after cataract surgery. *Am J Ophthalmol.* 2014;157:1144–1150.e1.
- Kosker M, Duman F, Suri K, Hammersmith KM, Nagra PK, Rapuano CJ. Long-term results of keratoplasty in patients with herpes zoster ophthalmicus. *Cornea.* 2013;32:982–986.
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet.* 2006;367:1618–1625.
- Kinard KI, Smith AG, Singleton JR, et al. Chronic migraine is associated with reduced corneal nerve fiber density and symptoms of dry eye. *Headache.* 2015;55:543–549.

12. Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. Neurobiology of migraine. *Neuroscience*. 2009;161:327-341.
13. Digre KB, Brennan KC. Shedding light on photophobia. *J Neuroophthalmol*. 2012;32:68-81.
14. Dolgonos S, Ayyala H, Evinger C. Light-induced trigeminal sensitization without central visual pathways: another mechanism for photophobia. *Invest Ophthalmol Vis Sci*. 2011;52:7852-7858.
15. Okamoto K, Tashiro A, Chang Z, Bereiter DA. Bright light activates a trigeminal nociceptive pathway. *Pain*. 2010;149:235-242.
16. Moulton EA, Becerra L, Borsook D. An fMRI case report of photophobia: activation of the trigeminal nociceptive pathway. *Pain*. 2009;145:358-363.
17. Moulton EA, Becerra L, Rosenthal P, Borsook D. An approach to localizing corneal pain representation in human primary somatosensory cortex. *PLoS One*. 2012;7:e44643.
18. Siqueira SR, Siviero M, Alvarez FK, Teixeira MJ, Siqueira JT. Quantitative sensory testing in trigeminal traumatic neuropathic pain and persistent idiopathic facial pain. *Arq Neuropsiquiatr*. 2013;71:174-179.
19. Falace DA, Reid K, Rayens MK. The influence of deep (odontogenic) pain intensity, quality and duration on the incidence and characteristics of referred orofacial pain. *J Orofac Pain*. 1996;10:232-239.
20. Drummond PD. Photophobia and autonomic responses to facial pain in migraine. *Brain J Neurol*. 1997;120(pt 10):1857-1864.
21. Shibuta K, Suzuki I, Shinoda M, et al. Organization of hyperactive microglial cells in trigeminal spinal subnucleus caudalis and upper cervical spinal cord associated with orofacial neuropathic pain. *Brain Res*. 2012;1451:74-86.
22. Sikandar S, Dickenson AH. Visceral pain: the ins and outs, the ups and downs. *Curr Opin Support Palliat Care*. 2012;6:17-26.
23. Li Y, Dorsi MJ, Meyer RA, Belzberg AJ. Mechanical hyperalgesia after an L5 spinal nerve lesion in the rat is not dependent on input from injured nerve fibers. *Pain*. 2000;85:493-502.
24. Sang CN, Gracely RH, Max MB, Bennett GJ. Capsaicin-evoked mechanical allodynia and hyperalgesia cross nerve territories. Evidence for a central mechanism. *Anesthesiology*. 1996;85:491-496.
25. Sessle BJ. Neural mechanisms and pathways in craniofacial pain. *Can J Neurol Sci*. 1999;26(suppl 3):S7-S11.
26. Sessle BJ, Hu JW, Amano N, Zhong G. Convergence of cutaneous, tooth pulp, visceral, neck and muscle afferents onto nociceptive and non-nociceptive neurones in trigeminal subnucleus caudalis (medullary dorsal horn) and its implications for referred pain. *Pain*. 1986;27:219-235.
27. Ugurlu S, Bartley GB, Otley CC, Baratz KH. Factitious disease of periocular and facial skin. *Am J Ophthalmol*. 1999;127:196-201.
28. Sandrini G, Alfonsi E, Ruiz L, et al. Impairment of corneal pain perception in cluster headache. *Pain*. 1991;47:299-304.
29. Belmonte C, Acosta MC, Merayo-Llodes J, Gallar J. What causes eye pain? *Curr Ophthalmol Rep*. 2015;3:111-121.