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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1167/iovs.16-20557</td>
</tr>
<tr>
<td>Accessed</td>
<td>April 2, 2018 3:26:02 AM EDT</td>
</tr>
<tr>
<td>Citable Link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:29408203">http://nrs.harvard.edu/urn-3:HUL.InstRepos:29408203</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>

(Article begins on next page)
Oculofacial Pain: Corneal Nerve Damage Leading to Pain Beyond the Eye

Perry Rosenthal, David Borsook, and Eric A. Moulton

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.

Perspectives

Recent studies suggest that many cases of dry eye (DE) have evidence of neuropathic pain that arises from chronic disorders, 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, corneal cross-linking for keratoconus, cataract surgery, lamellar keratoplasty, 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, 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. 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 cortex 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, 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, suggesting complex interactions across multiple levels of the trigeminal system. Similarly, photophobia...
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.23 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 structures that have been labeled as 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 and/or thalamus.25 From here, second-order neurons project to the primary somatosensory cortex where the cornea is functionally represented. The boxes below show referred pain (trigeminothalamic tract) to nuclei within the thalamus (e.g., ventroposterior-medial thalamus). From here, third-order neurons project to the 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.

![Trigeminal convergence pathway for oculofacial pain](image)

**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., ventroposterior-medial 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 and (right) to orofacial viscera from the cornea and skin.


