The fever of pain: ocular chronic pain, light at the end of the tunnel

A febre da dor: dor ocular crônica, uma luz no fim do tunel

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"Dogma says: believe the data that fit your model of the world and ignore the rest.
The world says, ignore the dogma and extend your model to fit the world."
Amit Goswami, "Quantum creativity: think quantum, be creative"

One of the most depressing situations in the outpatient clinic occurs when an individual describes a long-term incurable pain condition along with a never-ending list of unhelpful exams and treatments. Worse, when our complementary exams confirm the previous clinical impressions: no signs of inflammation, and no clues about a trigger or a possible cause.

The classic presentation of inflammation has four elements: redness, swelling, heat and, the pain, reasonable consequence of the previous three. In "the most densely innervated organ of the body", the cornea[1,2], pain, is frequently observed without the other elements of inflammation. The explanation is: neuropathic pain. Although it has a multidimensional clinical expression and is present in other conditions, such as absolute glaucoma; chronic corneal pain is receiving more awareness, and the reasons are commented below.

In 2010, Perry Rosenthal et al., started clarifying and discussing clinical support for patients under chronic corneal pain. Since their initial work, readers can find reports on what they have defined as "pain without stain", and labeled as corneal neuropathic pain or keratoadinia[3,4]. This authors supplied their working hypothesis on the potential triggers, possible pathways and why keratoadinia has been confused with dry eye disease. Both diseases are often seen in a comprehensive ophthalmic clinic, present with discordant signs and symptoms and in general there is no much to offer, except chronic medication to modestly relief for the discomfort[5]. Moreover, they have shown that several diseases beyond herpetic and diabetic neuropathic syndromes can affect the eye leading to both dry eye and neuropathic corneal pain[6,7].

In the daily practice, practitioners face differential diagnoses between keratoadinia and malingering, somatic syndromes or hysteria, which are out of the scope and expertise of ophthalmologists. In a typical scenario, a patient would have consulted more than two ophthalmologists in a recent period and presents with diagnosis and treatment of other unrelated syndromes, such as chronic fatigue, irritated bowel syndrome, and fibromyalgia[8]. Some of those medications present confusing anti-cholinergic effects that may hamper the correct diagnosis.

Those patients are more frequently 40 to 50 years-old women, living in deprived areas, but keratoadinia can be found in males and younger individuals from more affluent areas[9]. The condition itself can impact learning and carrier progression, as well as social and daily life activities. It is also challenging to conduct those cases, due to the lack of credibility on medical resources created by previous unsuccessful evaluations and treatments with confounding side effects.

Are there good news at the front? The answer is yes! Several papers and presentations in recent years are clarifying the details of so called "cornea pain without stain". Great contributions are coming from neurophysiology and molecular biology, revealing the players (membrane receptors in the cornea and neural routes) of pain induced by minor interventions and drugs, associated or not with chronic diseases[10-12].

Recent advances have facilitated the *in vivo* observation of corneal nerves, using different Optic Coherence Tomography strategies for confocal microscopy. It is not surprising that changes in the format and density of corneal nerves observed in various conditions associated with ocular pain and/or dry eye are now established as markers of this unique complex disease: the neuropathic corneal pain[3]. The decreased total number of nerves and the presence of trunks, branches, shorter length, and higher tortuosity were correlated with lower tactile sensation[13-16]. Moreover, it is now proven that corneas lacking healthy nerves have more inflammatory cells and are prompt to new vessels[17].

Were you skeptic about sympathetic ophthalmia? Believe now: clinical and histologic observations revealed that unilateral corneal damage induces bilateral changes to corneas and also to both trigeminal ganglion[13,14,17,18]. So why not uveitis? Let me explain: those peripheral nerves seen in the cornea are dendrites of cell bodies located in the trigeminal ganglion in the brain and they cross-talk with the opposite side.

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The link among inflammatory response, cornea innervation, pain and involvement of the opposite side (the contralateral untouched eye in a trauma, for example) was not clear until the effects of cornea wound in the central nervous system was investigated (more specifically the route of the trigeminal nerve and its ganglion). The findings were striking. An elegant study conducted by Dr. Paolo Rama and his group revealed that an alkali burn lead to inflammation in both trigeminal ganglions of the injured mice[18]. They confirmed previous similar findings observed with herpes infection, a well-known disease that interplays the cornea and the trigeminal nerves[19]. Ironically, it was reported more than 80 years ago, that vitamin deficiency is not directly challenging for the cornea structure and tears secretion, but it would be associated with damages to the trigeminal ganglion[20].

In summary, in the central nervous system, higher-order neurons structures can be inflamed and altered after an ocular surface damage. The nerve inflammation can perpetuate and appear as a painful but apparently not injured eye. The cornea nerves and the trigeminal ganglion once injured become highly sensitized but are still not visible at gross examination. This disjoined process occurs in different conditions and in a dissimilar way in different individuals, depending on demographic and genetic backgrounds[21,22]. Putting together, these findings open avenues for the clarification of the chronic neuropathic cornea pain mechanisms, and start showing us a light at the end of the tunnel for better treatment and hence restoring patients' confidence. To reach the light on neuropathic pain related to the ocular surface, eyes should be investigated as the windows to the brain.

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