Case report

Gabapentin for presumed neuropathic ocular pain

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ABSTRACT

Purpose: To report a case of chronic neuropathic ocular pain in a patient without visual complaints.

Observations: A 37-year-old male with a history of bilateral laser-assisted in situ keratomileusis (LASIK) presented with pain symptoms of 8 months duration in the left eye. The prior LASIK surgery was complicated by corneal ectasia in the left eye requiring penetrating keratoplasty and subsequent placement of a glaucoma drainage implant for uncontrolled, elevated intraocular pressure. The patient was evaluated with a complete clinical examination, including Goldmann applanation tonometry, dilated fundus examination, fluorescein angiography, optical coherence tomography, and magnetic resonance imaging. After 3 weeks of treatment with gabapentin 300 mg BID, the patient reported complete resolution of the ocular pain.

Conclusions and Importance: The pathophysiology of neuropathic ocular pain remains poorly understood. Clinical evaluation often reveals minimal ophthalmic exam findings, leading to an underdiagnosis of the condition by ophthalmologists. Gabapentin may be an underutilized medication in the treatment of chronic ocular pain.

1. Introduction

Chronic pain syndromes affect over 100 million adults in the United States with an estimated economic impact of $150 billion annually in medical care costs and lost productivity. Chronic pain can present in many ways: most commonly with pain in the back (10.1%), lower extremity (7.1%), upper extremity (4.1%), and headaches (3.5%). Chronic ocular pain affects 15% of the United States population. The wide variety of conditions encompassed by these categories are poorly understood and, as a result, lack established management guidelines. Optimal management, which involves a multi-disciplinary team, only reduces pain by about 30% on average. Approaches to treatment include pharmaceuticals, physical medicine, behavioral medicine, neuromodulation, and surgery. Ultimately, the suffering caused by these syndromes and their intractability can affect patients’ social, recreational, and occupational functioning through negative effects on mood, sleep, exercise, and activities of daily living. We present a case of presumed neuropathic ocular pain successfully treated with gabapentin.

2. Case report

A 37-year-old man presented with a history of laser-assisted in situ keratomileusis (LASIK) in 2007 which was complicated by progressive ectasia requiring a penetrating keratoplasty (PKP) in the left eye in 2013. His past medical history included type 2 diabetes mellitus (without neuropathy), obesity, and obstructive sleep apnea for which he was taking liraglutide and lorcaserin. He had no prior history of headache syndrome, anxiety, or depression. Six months after his initial presentation in 2013, he presented with acutely elevated intraocular pressure and underwent implantation of a Baerveldt glaucoma drainage implant (Johnson and Johnson Vision, Jacksonville, FL, USA). The patient had consistently worn a scleral contact lens (SCL) over this time period without issues until a follow-up visit in October 2016, during which he complained that the lens was uncomfortable and “wants to pop off.” At a May 2017 appointment, he described a pronounced left eye pain characterized as a dull ache without associated redness, light sensitivity, or vision changes. He endorsed using dorzolamide/timolol, loteprednol, and artificial tears in the left eye. The pain was associated with left-sided headaches, localized to the left temple region. Five months after initial pain presentation, he was able to further characterize the pain as a waxing and waning, retrobulbar ache. By this point, he also endorsed redness and swelling of the left eye. The patient’s ocular pain was refractory to office treatment with topical preprocaraine.

Examination of the left eye at the time of pain presentation was significant for a visual acuity of 20/20 with contact lens correction, intraocular pressure of 20 mm Hg and equal, reactive pupils without an

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afferent pupillary defect. His extraocular motility and confrontational visual fields were full. On slit lamp exam of his left eye (Fig. 1), he had mild ptosis, a well-covered glaucoma drainage implant plate and tube, trace injection of the conjunctiva, clear PKP, and a deep and quiet anterior chamber. The fundoscopic exam of the left eye demonstrated a 0.3 cup-to-disc ratio, a sharp foveal light reflex, and normal retinal vasculature and periphery. Subsequent follow-up visits over the next few months showed an ocular surface exam of the left eye significant for intermittent 1+ Meibomian gland dysfunction and blepharitis without corneal epithelial disruption, and intermittent 1+ flare in the anterior chamber. Slit-lamp examination of the right eye was entirely within normal limits.

Six weeks after his initial pain presentation, the patient explained that the pain severity was increasing and limiting his normal work functions and interfering with sleep. He described an associated “burning” sensation as the most intense feature of his pain. The patient was subsequently evaluated by cornea, uveitis, oculoplastics, and optometric subspecialists to rule out corneal pain, scleritis, and other causes of pain, respectively. Magnetic resonance imaging (MRI) of the brain and orbit showed an enlarged left lacrimal gland. However, on history and physical examination no signs or symptoms of inflammation were elicited, and thus, this MRI finding remained clinically incompatible with dacyroadenitis. A uveitis work-up examination noted tenderness over the aqueous shunt bleb but was ultimately negative for posterior scleritis, including normal B-scan ultrasonography findings (Fig. 2). The pain was refractory despite a three-month trial and subsequent discontinuation of ibuprofen 800mg three times daily and only temporarily alleviated by fluorometholone twice daily OS and oral prednisone 60mg daily. Approximately eight months after initial pain onset, the patient was started on gabapentin 300mg twice daily. After 3 weeks on this therapy, he reported his pain as a “0 out of 10.” He was subsequently able to tolerate normal wear of his SCL.

3. Discussion

Eye pain can involve the globe itself or the surrounding structures. Depending on its origin, eye pain can be described as dull, sharp, burning, shooting, throbbing, pressure, or a foreign body sensation. Eye pain can also mimic other causes of pain from nearby structures, such as headaches, sinus pain, or toothaches. Associated signs and symptoms can include loss of vision, photophobia, tearing, halos, floaters, limitation of eye movement, redness, pupillary defect, proptosis, edema, and tenderness. The differential diagnosis is broad, and includes conjunctivitis, chemical burns, blepharitis, chalazion, iritis, acute angle closure glaucoma, optic neuritis, trauma, and corneal abrasions.

As with other types of pain, chronic ocular pain can be nociceptive and/or neuropathic in nature. Nociceptive pain is defined as pain originating from damage to tissue resulting in activation of a neural pathway. It occurs from a source outside of the nervous system and can be inflammatory, compressive, or traumatic. Conversely, neuropathic pain originates from a lesion or dysfunction of the somatosensory nervous system. Neuropathic and nociceptive pain can result independent of one another, or on a continuum, with chronic nociceptive pain leading to neuropathic pain through effects on neural plasticity.

For this reason, it may be necessary to first treat all possible causes of nociceptive pain before ruling pain to be neuropathic in nature and treating accordingly. An anesthetic drop helps to distinguish between the two, with simple nociceptive pain often diminishing on instillation. Our patient did not have frank signs of ocular inflammation but was treated with topical anti-inflammatory agents before treatment of presumed ocular neuropathic pain.

Corneal refractive surgery may also lead to a combination of nociceptive and neuropathic pain. Ocular surface discomfort following corneal refractive surgery was previously thought to result from effects of dry eye disease. However, further elucidation of the role neuroplasticity plays in the development of neuropathic pain has shown that the direct nerve damage attributed to corneal surgery leads to long term effects on the somatosensory nervous system. Of note, our patient’s complaint of ocular surface symptoms did not begin after LASIK, but rather after aqueous shunt implantation.

Neuroplasticity can result in changes in both peripheral and central neurons leading to hyperalgiesia and allodynia. These changes, known as sensitization, may be precipitated by chronic nociceptive pain. Peripheral sensitization often results from inflammatory cytokines released during tissue injury, while central sensitization results from complex feedback loops within the central nervous system that augment somatosensory pain signaling. The exact causal mechanisms of chronic neuropathic ocular pain remain to be fully described. First, damage to peripheral ocular nerves causes upregulation of voltage-gated sodium channels within individual neurons, thus decreasing the threshold for transduction of signals, including those of pain. Second, pain also affects N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptors which, through unknown mechanisms, both increase activation of ascending pain pathways and decreases activation of descending inhibitory pathways. Part of this mechanism includes increased responsiveness and density of these receptors following constant exposure to excitatory nociceptive input, as well as changes in chloride currents of GABA receptors leading to decreased inhibitory influence of these receptors on ascending pain pathways. Stress, depression, anxiety and mood disorders may contribute to neuropathic pain through central modulation and remodeling effects. Finally, impaired defenses against environmental insults may also contribute to hyperalgiesia and allodynia.

Treatments for neuropathic pain have been better studied in diabetic neuropathy, post-herpetic radiculopathy, nerve compression or trauma, and autoimmune diseases and therefore may provide insight in the treatment of chronic neuropathic ocular pain. In a study of 57 patients with chronic neuropathic pain by Gilron et al., gabapentin was superior to placebo for improving self-reported pain, depression, and physical functioning after 4 weeks. A Cochrane review of 37 studies of 5914 patients demonstrated substantial benefit of gabapentin for reduction of chronic pain in post-herpetic neuralgia, diabetic neuropathy, and other
neuropathic pain conditions.\textsuperscript{13}

Though Gabapentin remains well established as a first-line treatment for diabetic neuropathy,\textsuperscript{7,8,15} few randomized control studies have examined the utility of the drug in corneal neuropathic pain.\textsuperscript{16} Ongun et al. showed a decrease in patient reported pain in a cohort of patients with chronic corneal neuropathic pain and dry eye disease treated with gabapentin compared to a placebo group.\textsuperscript{17} Other randomized control studies examining the efficacy of gabapentin in treating ocular pain in post-photorafactive surgical patients have revealed mixed results. Lichtinger et al. showed a decrease in patient reported post-operative pain with the use of gabapentin.\textsuperscript{18} Another study revealed that patients treated with a combination of gabapentin and pregabalin experienced decreased pain following photorefractive keratectomy (PRK).\textsuperscript{19} Kuhnle et al. revealed no difference in post-operative pain after PRK in patients treated with gabapentin compared to placebo.\textsuperscript{20} Of note, each of these study designs incorporated dosing schedules below the recommended initial dosage of 1200mg daily of gabapentin for neuropathic pain. Nonetheless, the exact link between post-surgical corneal pain and chronic neuropathic ocular pain remains unclear.

A prior case report by Kavalieratos and Dimou demonstrated successful pain management of a blind glaucomatosus eye with gabapentin after 6 months of treatment.\textsuperscript{21} Similarly, we present a case of chronic ocular pain treated successfully with low-dose gabapentin. The case described herein involves a lower treatment dose than described in the literature. However, our patient’s ocular pain and headache immediately subsided after this intervention and therefore was unlikely to be attributed to spontaneous resolution.

Patients presenting with complaints of headache can be difficult to efficiently diagnose, as the differential diagnosis requires large Eye pain often presents concurrently with headaches. A broad, though not exhaustive, differential for headache with eye pain includes ocular surface disease, asthenopia, intermittent angle closure glaucoma, intraocular inflammation associated with uveitis, primary trochelear headache, cluster headaches, migraine headaches, giant cell arteritis, idiopathic intracranial hypertension, depression, and anxiety.\textsuperscript{22,23} A thorough history and physical will assist the astute clinician in identifying the likely etiology of patients presenting with complaints of eye pain and headache. Workup should include an in-depth ocular surface exam, with findings and history guiding appropriate imaging modalities.

The Ocular Pain Assessment Survey (OPAS) is a validated questionnaire that helps assess the severity of ocular pain and its effect on patients’ quality of life.\textsuperscript{24} The survey includes questions regarding eye pain, non-eye pain, quality of life factors, and other associated symptoms. The tool can be included with the ocular surface disease index (OSDI) to characterize surface disease and may be utilized at initial encounters and subsequent follow-ups to assess pain progression and response to treatment. Further testing, including the proparacaine challenge test, corneal esthesiometry, and in vivo corneal confocal microscopy may help localize the ocular pain.\textsuperscript{24} Treatment should be tailored to the likely precipitant, including aggressive lubrication and/or autologous serum tears for ocular surface disease and anticonvulsants for cases of neuropathic pain.\textsuperscript{25,26} Various psychiatric medications including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are also effective, though with increased side effect profiles, particularly with the use of TCAs.\textsuperscript{27,28}

The association of neuropathic ocular pain and psychiatric disorders has been well-established. Patients with depressive symptoms were found by Far et al. to have increased prefrontal activation and resultant decreased pain thresholds.\textsuperscript{29} In a case-control study, Hallak et al. identified a positive correlation between depressive symptoms and symptoms of dry eye disease.\textsuperscript{30} In light of these findings, for patients with neuropathic ocular pain, it may be beneficial to perform a thorough social and psychiatric history and consider a referral for psychiatric evaluation. Our patient’s evaluation for anxiety and depression was negative.

4. Conclusion

Chronic ocular pain is a complicated and poorly understood condition. We report a 37-year-old male presenting with constant left eye pain associated with headaches, whose pain was successfully reduced after 3 weeks of treatment with gabapentin. Our case and literature review highlight the importance of gabapentin and thorough psychosocial evaluations in patients with chronic neuropathic ocular pain.

Patient consent

As this was a retrospective chart review and all unique patient identifiers were eliminated, patient consent was neither required nor obtained for this case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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