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Evidence that dry eye represents a chronic overlapping pain condition

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Abstract

Recent data suggest that corneal somatosensory dysfunction may be the underlying cause of severe dry eye symptoms in the absence of ocular surface pathology seen in a subset of patients diagnosed with "dry eye syndrome." This subset of patients tends to demonstrate a unique constellation of symptoms that are persistent, more severe, and generally respond poorly to current dry eye therapies targeting inadequate or dysfunctional tears. A growing body of literature suggests that symptoms in these patients may be better characterized as neuropathic ocular pain rather than dry eye. In these patients, dry eye symptoms are often associated with numerous comorbid pain conditions and evidence of central pain processing abnormalities, where eye pain is just one of multiple overlapping peripheral manifestations. In this review, we discuss the concept and potential mechanisms of chronic overlapping pain conditions as well as evidence for considering neuropathic ocular pain as one of these overlapping pain conditions.

Keywords

Dry eye, neuropathic pain, central sensitivity, peripheral sensitivity, chronic overlapping pain conditions, neuropathic ocular pain, genetics, chronic widespread pain, fibromyalgia, irritable bowel syndrome, vulvodynia, and temporomandibular disorder

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Introduction

The diagnosis of dry eye (DE) is commonly applied to patients with complaints of visual disturbances, tearing, ocular discomfort, and photophobia. This diagnosis is extremely common and a source of significant morbidity given approximately 15% of Americans are affected,[1,2] and patients with severe DE symptoms have utility scores (a measure of physical, mental, and social functioning) similar to patients with moderate to severe angina.[3] However, DE is a heterogeneous diagnosis, and this umbrella term covers a host of symptoms with many potential underlying etiologies.[4] The standard clinical approach to addressing DE is to treat for tear dysfunction. However, it is well documented that symptom severity correlates poorly with ocular surface signs and tear film parameters,[5] and current treatments focused on tear replacement do not adequately control symptoms in many patients.[6] Recent data suggest that, in some patients, somatosensory dysfunction may explain severe DE in the absence of ocular surface abnormalities.[7,8] There is a growing body of literature suggesting that DE symptoms in these patients may be better conceptualized as neuropathic ocular pain (NOP),[9–11] and that

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NOP may be the expression of a central pain processing disorder, where eye pain is just one of multiple overlapping peripheral manifestations. In this review, the concept and potential mechanisms of chronic overlapping pain conditions (COPC) will be discussed, and the evidence for considering NOP, one of these overlapping conditions will be presented.

Some DE patients may be better characterized as suffering from NOP

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[12] Based on this broadly accepted definition, many DE symptoms, such as burning or aching, qualify as manifestations of ocular pain. Characteristics of ocular pain overlap with descriptors of pain elsewhere in the body and have been effectively captured with non-ocular pain questionnaires.[13,14] These include the McGill Pain Questionnaire,[15] and the Neuropathic Pain Symptom Inventory, modified where necessary for eye-specific pain phenomena (e.g., eye pain evoked by wind, hot/cold, or light).[9–11,16]

Pain is typically classified into two categories: nociceptive and neuropathic. Nociceptive pain generally arises from the damage of non-neural tissues such as skin, muscle, or bone following injury or inflammation. Neuropathic pain arises from damage or dysfunction within the nervous system. Nerve damage can arise from trauma (including surgical trauma), infection, autoimmune attack, genetic predisposition, or other causes. Typical features of neuropathic pain include burning, shooting, or electric quality of pain; local sensory deficit; hyperalgesia (increased pain response to noxious stimuli); allodynia (elicitation of pain by innocuous stimulus, such as light touch); and spontaneous pain. Neuropathic pain may also be reported in the apparent absence of ongoing peripheral pathology.[17]

Multiple studies have shown that a significant subset of DE patients describe symptoms consistent with NOP.[9,11,18,19] These specific symptoms include hypersensitivity to light (e.g., photophobia), wind, and heat or cold (manifestations of allodynia and hyperalgesia in the eye), spontaneous burning eye pain, and pain to pressure and light touch (including application of Schirmer's test strips). NOP symptoms, specifically hot burning pain and wind hyperalgesia, are significantly correlated with a lack of response, or partial response, to artificial tears.[18] As these drops replace the tear layer and do not address any underlying neuropathology, a lack of therapeutic response in these DE patients may suggest that their symptoms are not due to abnormalities in tear film or the ocular surface. It is well known that ocular surface pathology and clinical signs of DE do not correlate with the presence or severity of symptoms in many patients. In a Veterans Affairs cohort, DE symptoms (as measured by the Dry Eye Questionnaire-5 and Ocular Surface Disease Index [OSDI]) were found to align more closely with non-ocular pain and post-traumatic stress disorder scores than any objective signs on physical exam, accounting for 36% and 40% of variability in questionnaire scores, respectively.[10] This disconnect is also seen in the setting of post-LASIK "DE," where symptoms of ocular pain often manifest and persist chronically following the significant nerve damage incurred during surgery, even in the setting of a normal ocular surface exam.[7,8,20] Thus, DE symptoms unresponsive to drops may be associated with neuronal dysfunction associated with pathologic neuroplasticity.[21]

Somatosensory dysfunction is another key feature of neuropathic pain that is seen in many DE patients. A classic example of neuropathic pain is the diabetic patient who reports spontaneous shooting pains in their feet and legs, but on exam they are found to have reduced sensation in the same region. An analogous situation may be seen in the eye after the nerve damage induced by the LASIK surgical procedure for vision correction that severs corneal nerves.[8] For example, a prospective series of 48 patients found that corneal hypoesthesia was associated with more severe DE symptom scores.[22] This phenomenon is not limited to LASIK-associated DE. As a group, patients with Sjogren's Syndrome and non-Sjogren's Syndrome associated DE have been found to have altered somatosensory function, in the form of corneal hyper- or hypoesthesia.[16,23–27] The conjunctiva is also innervated by the trigeminal nerve, primarily V1, although V2 also plays a role. However, the role of conjunctival nerves in the propagation of ocular pain has not been described in literature.[28]

Other data demonstrate an expansion of the receptive field to contiguous areas within the distribution of the trigeminal system, a phenomenon typically associated with maladaptive neuroplasticity within the central nervous system (CNS) associated with chronic pain.[29] When adaptive neuroplasticity in the somatosensory system is persistent beyond the normal protective role and is associated with chronic pain, it represents *pathologic neuroplasticity*.[30] There is also evidence that in patients with severe DE, this neuronal dysfunction is not limited to the trigeminal system, but present systemically, as evidenced by altered somatic (e.g., forearm) pain sensitivity thresholds.[31] These findings are *prima facie* evidence that some forms of DE are associated with widespread changes in the CNS, which may help to explain why chronic DE symptoms are often observed as comorbid with multiple other pain and mental health conditions. This topic is developed in more detail in subsequent sections; however, these findings underscore the importance of looking

beyond the ocular surface in those patients with suspected DE who demonstrate evidence of somatosensory dysfunction.

For additional information and development of the concept of NOP, the writers refer you to the recently published review by Rosenthal and Borsook[32]

DE and chronic pain syndromes tend to co-exist and share features of pathologic neuroplasticity

The ability of the nervous system to adapt in response to stimuli is known as neuroplasticity. *Pathologic neuroplasticity* can occur in the peripheral or central somatosensory systems. Typically, the inflammatory milieu resulting from peripheral nerve injury induces nociceptor hypersensitivity through a process called peripheral sensitization, which results in decreased thresholds for nociceptor excitation. These changes may be perpetuated by corresponding changes in the CNS well after the initial injury has resolved.[29] At some point, these changes cease to play a physiologic role and instead maintain a pathologic pain state.[21,33] Clinically, this neuroplasticity results in the spontaneous pain, allodynia, hyperalgesia, and potentially persistent pain after the resolution of the initial injury. The specific mechanisms implicated in these processes are discussed in detail later in this review. In this context, the discordance between peripheral signs and symptoms, lack of response to local treatment, and evidence of local and systemic alterations in pain processing in DE are consistent with the idea that symptoms of NOP are not necessarily maintained by pathology at the ocular surface but somewhere higher in the nervous system. This phenomenon is not unique; there is a constellation of chronic pain disorders that are hypothesized to be related through a mechanism of central somatosensory dysfunction. These have been referred to as ''chronic overlapping pain conditions.''[34] COPC are a cluster of commonly comorbid syndromes including temporomandibular joint disorder (TMD), osteoarthritis, chronic fatigue, irritable bowel syndrome (IBS), interstitial cystitis, fibromyalgia/chronic widespread pain (CWP), endometriosis, chronic headache, migraine, and chronic low back pain.[35] These disorders manifest in various parts of the body and are united clinically by a few key features: epidemiologic data demonstrating a tendency to co-exist in the same patients, greater prevalence in women, and association with other comorbidities including mood disorders, sleep abnormalities, and decreased quality-of-life.[36–39] Historically, these pain disorders have been characterized as ''functional'' in nature due to the absence of identifiable end-organ pathology[35]; however, as our understanding of chronic pain improves, this distinction is it is quickly losing validity, especially as the concept of central pain processing disorders continues to develop.[9,38,39]

COPC is an evolving concept in the literature. Between 1995 and 2014, the number of publications investigating the relationships between two or more currently recognized COPC increased fivefold.[35] As epidemiologic and mechanistic evidence mounts that these conditions are related, it has become clear that rather than distinct co-existing diseases, these conditions are better conceptualized as multiple presentations of one underlying disorder. Relatively strong heritability data further suggest that these comorbid conditions run in families.[40–43] As a consequence, this cluster of conditions is believed to share genetic factors as common underlying risk factors,[36–39] and it is hypothesized that these conditions are peripheral manifestations of somatosensory dysfunction caused by a central pain processing disorder.[9,38,39]

There are many apparent similarities between the currently recognized COPC and DE. As in some individuals with DE, it can be difficult to treat the peripheral pain manifestations in patients with COPC, with no treatment modality effective in all cases.[35] The epidemiology of COPC and DE is also similar. The prevalence of COPC ranges from 2% to 10% in applicable patient populations, and while the prevalence of DE is difficult to determine because of variability in definition, studies estimate its prevalence at 5.7% to 9.8% in women and 3.9% to 7.7% in men, depending on age.[44,45] The prevalence and incidence of COPC and DE are higher in women.[46] Female sex is a risk factor for persistent DE after corneal nerve injury associated with the LASIK procedure (vision correction) and links this type of persistent pain to other forms of chronic pain that occur more often in females after surgical nerve injuries.[47,48] Finally, DE and other COPC are strongly associated with affective disorders such as PTSD, anxiety, depression,[46,49,50] and insomnia attendant with psychological stress and pain amplification.[51–56]

As discussed above, there is increasing evidence that patients with NOP tend to have co-existing COPC, and these patients exhibit a distinct and more severe DE phenotype. A series of studies in a Veterans Affairs population indicate that more severe symptoms consistent with NOP are associated with more severe symptoms and greater numbers of chronic pain conditions elsewhere in the body, including higher overall non-ocular pain intensity; and these findings are associated with more abnormal mental health scores.[57] Likewise, these investigators found that patients with greater numbers of concomitant chronic pain syndromes had more severe DE symptoms consistent with NOP.[9] In both cases, objective ocular surface signs were not significantly different between groups. An independent investigation, working with a population of tertiary care DE patients in the Netherlands, found that 17% had at least one

chronic pain syndrome (which included IBS, chronic pelvic pain, and CWP).[58] Once again, patients with comorbid pain syndromes had more severe symptoms and scored higher on every OSDI subscale, and there was no difference in ocular signs between study groups.[58]

Evidence that somatosensory dysfunction underlies both COPC and DE

Dysfunction in the corneal somatosensory apparatus associated with ocular pain may manifest as either corneal hyper- or hypoesthesia.[12,16,22,25,59,60] Increased sensory sensitivity may also be captured by questionnaires in addition to physical examination. The Pain Sensitivity Questionnaire is a validated tool used in chronic pain research, which provides a rating of pain sensitivity by prompting the taker to imagine themselves in various potentially painful situations (i.e., picking up a hot pot with bare hands). A recent study found that higher Pain Sensitivity Questionnaire scores were found to significantly correlate with higher OSDI scores, lower average end-of-day comfort, and greater end-of-day dryness in patients with ocular discomfort induced by wearing inverted contact lenses.[61] There is also increasing evidence that a subset of DE patients experience pain in other areas within the distribution of the trigeminal system in addition to the ocular surface, such as the orbit, ears, and other parts of the face. It is hypothesized that this syndrome of *oculofacial pain* perhaps represents pathologic neuroplasticity within the trigeminal systems displayed as an expansion of the nociceptive reflex field associated with chronic pain.[27] However, somatosensory dysfunction associated with DE is not limited to the trigeminal system, but seen systemically. Multiple studies describe patients with DE and more severe ocular pain demonstrate reduced tolerance to evoked pain on the forearm, a phenomenon indicative of a centralized somatosensory processing disorder.[31,59,62] Not surprisingly, this phenomenon is also seen in other COPC. For example, patients with IBS demonstrate widespread visceral and thermal hypersensitivity that is not localized to the abdominal region.[63] In general, COPC patients typically have lower pain thresholds and demonstrate systemically increased pain sensitivity across multiple nociceptive modalities (including pain induced by heat, cold, and ischemia)—derangements in pain perception that are not limited to a specific body site, consistent with widespread CNS somatosensory dysfunction.[34,35]

Potential mechanisms of pain processing disorders: Peripheral and central sensitization

As introduced earlier, central and peripheral hypersensitivity have been postulated as potential underlying mechanisms of the somatosensory dysfunction and pathologic neuroplasticity associated with chronic pain in patients with COPC and NOP. The processes of peripheral and central sensitization, respectively, describe the generation of enhanced nociceptor excitability in response to acute injury and the central maintenance of this increased pain response or generation of spontaneous pain after the resolution of any peripheral pathology. Taken together, these are important mechanisms for the development and maintenance of neuropathic pain throughout the body. Below we discuss the anatomy and pathophysiology of these processes as they may occur associated with DE.

Peripheral sensitization

The corneal epithelium is innervated by the primary sensory neurons of the subbasal nerve plexus. This plexus is composed primarily of unmyelinated C fibers with myelinated Aδ fibers also present to a lesser extent.[64,65] Data obtained from mice indicate that the three most prevalent types of corneal nociceptors are Aδ mechanoreceptors (comprising roughly 20%), which are responsible for acute pain transmission; polymodal nociceptors (70%), responsible for sensations transmitted through chemical, thermal, and endogenous inflammatory mediators; and C-fiber cold thermoreceptors (10%), which are temperature sensitive.[8,64–66] Damage to these superficial corneal nerves is thought to play a role in the development of DE and NOP.[27,66] The location of corneal nociceptors at the ocular surface makes them vulnerable to damage,[8,64–66] and repeated neuronal insult may result in maladaptive neuronal plasticity, nociceptor hypersensitivity, and the development of neuropathic pain.[21] These neuropathological changes, which include altered ion channel expression and functioning, reduced excitatory thresholds, and recruitment of nearby nociceptors beyond those injured (expansion of the nociceptive reflex receptive field) are referred to as peripheral sensitization[21,66–68] and are facilitated by increased release of proinflammatory mediators following tissue injury.[21,65,69] Although these mechanisms have not been studied extensively in the eye specifically, there is no evidence or apparent reason to assume that the mechanisms of the neuroplastic changes that occur after insult differ between the cornea and elsewhere in the body. Pathologic neuroplasticity associated with the development of chronic pain elsewhere in the body is well studied and can inform us about the process in DE.

A number of important mediators are associated with the development and propagation of persistent pain. These include the upregulation of transient receptor protein channels found on nociceptor terminals. Transient receptor potential vanilloid 1 (TRPV1) responds to stimuli from heat, chemicals, and abnormal pH.[66]

TRPV1 activation in response to hyperosmotic conditions has also been specifically studied in human corneal epithelial cells.[70] As a hyperosmotic environment is a common feature of DE,[71] TRPV1 channels may play an important role in the development and maintenance of the ocular pain experienced in DE. Upregulation of TRPV1 has been described in DE, interstitial cystitis,[72] and animal studies of fibromyalgia,[73] and it may play a role in mediating excitatory responses to the inflammatory mediators associated with DE symptoms.[69]

The inflammatory cascade involved in peripheral nerve injury also includes the recruitment of immune cells to the site of injury. Mast cells, neutrophils, and macrophages are involved in the release of tumor necrosis factor (TNF)α, interleukin (IL)1β, and other proinflammatory mediators that contribute to pain.[21,74] This barrage of infiltrating leukocytes, pain mediators, and activation of signaling molecules lead to neuronal nuclear reprogramming[75] resulting in upregulation of gene expression and altered neuronal excitability ultimately responsible for the peripheral sensitization and the development and persistence of neuropathic pain.[74] Local inflammation is known to be an important component of DE, and many of these mediators, including but not limited to TNFα, IL1, and IL6,[76,77] have been found in elevated levels in the tears of patients with DE. An increase in T cells has also been detected in the conjunctivae of DE patients,[78] indicating that immune cells are recruited to the ocular surface and may influence the ocular somatosensory system and contribute to pathologic neuroplasticity. A parallel situation has been described in IBS, where increased levels of IL-6, IL-1β, and TNF-α, as well as the recruitment of lymphocytes, neutrophils, and mast cells inside the bowel is described and may be involved in pathologic neuroplasticity in IBS.[79]

Central sensitization

Central sensitization can result from prolonged peripheral nerve damage and persistent inflammation leading to pathologic neuroplasticity of the CNS.[8,21,27,66–68,80] The neuronal changes leading to signal amplification and reduced nociceptor excitatory thresholds are similar to those seen in peripheral sensitization and include alterations in ion channels, signaling cascades, altered gene expression, and increased release of proinflammatory mediators. When these changes occur at the level of the CNS, the perception of pain may be dissociated from the initial peripheral stimulus and may also persist after the initial peripheral pathology has resolved.[21,66,67] This phenomenon may explain the well-described discordance between DE symptoms and signs on physical exam. These changes can also occur with primary damage to the CNS (e.g., traumatic brain injury), or arise without any identifiable initial injury.[9,66]

Potential mechanisms of peripheral and central sensitization

With regard to mechanisms that may explain the association between DE and other COPC, evidence suggests that both are associated with manifestations of systemic inflammation. Serum markers include IL-6, IL-1, TNF-a, and C-reactive protein (CRP). In particular, serum CRP elevations are linked with a constellation of diseases including diabetes mellitus, cardiovascular disease and myocardial infarction, asthma, osteoporosis,[81] and CWP.[81,82] A recent twin study has also demonstrated that elevated serum CRP levels, a biomarker of systemic inflammation, are also associated with increased evoked cold-pain sensitivity.[83]

Regarding the relationship specifically between DE and CRP, we reported previously that CRP does not correlate with tear film parameters in a predominantly male Veterans Affairs patient cohort.[84] However, more recent evidence supports the concept of a distinct NOP subset of DE patients, and this expanded dataset was recently reanalyzed with patients stratified by NOP symptoms and the number of comorbid chronic pain conditions. Similar to our prior publication, patients were placed by cluster analysis into two groups according to the prevalence of chronic pain conditions and pain locations. The Low Pain cluster ($N = 67$) had a lower number of reported pain complaints (number of comorbid pain conditions 2.6 ± 1.7 and number of pain locations 1.4 ± 1.0). The High Pain cluster ($N = 60$) had a higher number of overall reported pain complaints (number of comorbid chronic pain conditions 7.3 ± 3.6 and number of pain locations 4.2 ± 0.87). Significantly more patients in the High Pain cluster were found to have high CRP levels ($\geqslant 3$ mg/dL) compared to those in the Low Pain cluster (53% vs. 31%, respectively, $P = 0.012$). Furthermore, symptoms consistent with NOP were also correlated with an elevated CRP (Pearson $r = 0.24$, $P = 0.007$ for sensitivity to wind [range: 0–10]). Taken together, these new data demonstrate that patients with symptoms consistent with NOP and other overlapping pain conditions are more likely to have elevated serum CRP levels than their counterparts. Although the relationship remains unclear at this point, this link between systemic inflammation and DE is one potential explanation of the systemic alterations in pain processing seen in DE and other COPC.

Genetics: A critical connection between DE and other COPC

Shared genetic factors may ultimately explain the underlying mechanisms associated with the observed comorbidities among COPC, including the association between chronic pain conditions and frequently

co-existing mental health disorders, which contribute to psychological distress and pain amplification. Given the complex and heterogeneous phenotypes associated with these disorders, we are far from a complete genetic understanding of these conditions. However, recent compelling data begin to elucidate the underlying genetic architecture and molecular pathways involved in the shared pathogenesis of these conditions.

One large twin study out of the United Kingdom specifically studied the heritability of DE and other COPC. In a cohort of female monozygotic and dizygotic twins, estimates of the heritability of DE symptoms were about 30%, DE physician diagnosis was about 40%, and heritability varied from 25% to 80% for the various ocular signs of DE.[43] These heritability estimates are similar to those for other COPC, which range from about 40% to 70%.[40–42,85] These findings are consistent with the general finding that the heritability of pain sensitivity to various chemical, thermal, and mechanical stimuli is estimated at 22% to 60%.[86,87] Perhaps, the single most compelling piece of evidence for considering DE as a COPC comes from evidence that there are two shared genetic factors underlying the observed heritability for DE, IBS, CWP, and pelvic pain disorders. Results from this landmark study demonstrate that *shared latent genetic factors underlie COPC comorbidity* with an estimated heritability of 66%.[88] Additionally, as discussed above, previous studies identified genetic links between other COPC including CWP, pelvic pain, low back pain, and IBS, but *DE represents a new addition to this disease cluster*.[85]

Additional genetic data suggest potential biologic pathways and candidate genes associated with these COPC. Genetic polymorphisms in three biologic pathways have been implicated, including the adrenergic pathway, serotonin (5-HT) receptor expression and metabolism, and alterations in voltage-gated sodium channels. Within the adrenergic pathway, genetic polymorphisms associated with reduced catechol-O-methyltransferase activity and β2 receptor expression are associated with increased risk of CWP, IBS, interstitial cystitis, and TMD, as well as post-traumatic stress disorder, autonomic dysregulation, sleep issues, anxiety, depression, and alterations in pain modulation.[34,85,89] Serotonin is a neuropeptide known to contribute to peripheral sensitization and has been found at significantly higher levels in the tears of patients with both signs and symptoms DE disease as compared to those with only symptoms or signs.[90] Additional evidence for the role of serotonin in DE comes from recent studies linking the use of selective serotonin reuptake inhibitors with the development of DE symptoms and disruptions in tear film production and stability.[91,92] Genetic variations in the 5HT-2a and 5-HT transporter are associated with increased risk of the development of CWP, IBS, burning mouth syndrome, and TMD and are linked with personality and affective traits, somatic awareness, depression, and anxiety.[34,85] Polymorphisms in genes encoding sodium channels are also important in pain processing. SCN9A encodes the Nav1.7 sodium channel, a protein highly expressed in nociceptive neurons, and polymorphisms in this gene are associated with increased sensitivity to pain (erythromelalgia), as well as the development of CWP, TMD, osteoarthritis pain, and numerous comorbid conditions.[89,93–95] It remains unclear if biologic variability in any of these pathways explains shared genetic factors common to COPC disorders, including DE. Integrative genomic analyses with the capability to identify functional DNA variants that regulate gene expression will aid our understanding of those biologic mechanisms that are shared between COPC, and those that may be unique to a specific COPC.

Conclusions

DE represents a new member in the group of COPC. These conditions share clinical and epidemiological characteristics as well as genetic factors that determine biologic mechanisms of the underlying neuropathology. Given the comorbidities and significant impact on psychosocial functioning associated with COPC, it is important for the entire multidisciplinary medical team caring for these DE patients to adopt a holistic diagnostic and therapeutic approach to their chronic manifestations. Although satisfactory treatment for the majority of COPC is not yet available, adjusting our conceptualization of these diseases and recognizing the presence of an underlying systemic disorder are the first step to eventually establish effective diagnosis and treatments. This is particularly true for ''dry eye,'' a misnomer where the extent of systemic involvement in this disorder has, until recently, been underappreciated.

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