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Neuropathic Symptoms of the Ocular Surface: Dryness, Pain, and Itch

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Abstract

Purpose of review—To describe recent findings on epidemiology, pathophysiology and management of neuropathic symptoms of the ocular surface, with a focus on potential similarities between sensations of dry eye, pain and itch.

Recent findings—A narrative review of the literature was undertaken. Key references from research in dry eye, neuropathic symptoms of the ocular surface, ocular pain and itch as well as general references on itch and pain neurobiology were included. Recent findings suggest aspects of DE, chronic ocular pain, and itch symptomatology is driven by neuropathic pain mechanisms involving peripheral and central sensitization processes.

Summary—Ocular dryness, pain, and itch are prevalent complaints with several of shared features. Multiple lines of evidence suggest that peripheral and central neuronal sensitization processes are involved in generating and maintaining ocular sensory symptoms. Research is warranted on the epidemiology of ocular sensations, molecular mechanisms involved in nociception and pruriception in the eye, electrophysiological alterations in animal models of eye conditions, and therapeutic modalities that can alleviate unpleasant ocular sensations.

Keywords

Dry eye; pain; itch; peripheral sensitization; central sensitization; neuropathic pain

INTRODUCTION

Dry eye (DE) is a multifactorial disease with a high prevalence in the population worldwide. It was originally described as a salient feature of Sjögren's syndrome (SS) with patients

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reporting symptoms of dryness along with low tear production. It then expanded to include symptoms of dryness and/or ocular surface abnormalities in patients without SS [1]. In this group, however, symptoms of DE often do not correlate with ocular surface findings [2, 3]. Furthermore, when asked to characterize their ocular sensations, many individuals use additional descriptors, beyond dryness, to describe ocular symptoms. These include both spontaneous sensations such as burning, aching, and tenderness and evoked sensations such as pain in response to light and wind [4]. Notably, sensory descriptors applied by patients with DE resemble those applied by patients with painful peripheral neuropathies [1, 5, 6]. Many individuals with ocular conditions also report itch, sometimes occurring concurrent with pain [7, 8].

This is not surprising given potential shared underlying mechanisms between sensations of dryness, pain, and itch [9, 10]. This includes shared epidemiology, molecular mediators, electrophysiological findings, and response to therapeutics (Table 1). In this review, we will discuss these potential shared mechanisms and argue that neuropathic pain and nerve sensitization likely underlie the co-existence of these ocular symptoms.

THE EPIDEMIOLOGY OF OCULAR DRYNESS, PAIN, AND ITCH

The epidemiology of ocular dryness

Population based studies have examined the frequency of dryness sensations in US women and men. Of 36,995 Women's Health Study participants, 381 women (1.0%) reported experiencing dryness constantly, 2,109 (5.7%) often, 10,474 (28.3%) sometimes, and 24,031 (65.0%) never [11]. A similar study in 25,444 Physician Health Study participants found that 204 men (0.8%) experienced dryness constantly; 924 (3.6%), often; 4,716 (18.5%), sometimes; and 19,597 (77.0%), never [12].

The epidemiology of ocular pain

In the same populations, 207 (0.6%) women reported experiencing irritation constantly, 2,102 (5.7%) often, 18,901 (51.1%) sometimes, and 15,785 (42.7%) never.[11] Likewise, 126 men (0.5%) reported experiencing irritation constantly; 1,050 (4.1%), often; 10,622 (41.8%), sometimes; and 13,644 (53.6%), never.[12] Comparing these numbers, both dryness and irritation were more frequent and severe in women compared to men [13]. Another set of studies asked about the frequency (rarely, sometimes, often or all the time) of various ocular symptoms. Of 2,482 volunteers in the Salisbury Eye Evaluation study, approximately 33% reported grittiness and 25% reported burning sometimes, often, or all the time [14]. In an Australian study of approximately 890 participants, mild, moderate, or severe ocular discomfort was reported by 25% and photophobia by 50% [15].

Higher frequencies of DE symptoms (both dryness and pain) have been reported in hospital-based populations [2, 16]. We have used pain questionnaires to characterize the quality and severity of ocular pain in a hospital based population. The short-form McGill Pain Questionnaire (sf-MPQ) [17] characterizes the severity (mild, moderate, severe) and quality of pain using 15 descriptors (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting, tiring-exhausting, sickening, fearful, and/or

punishing-cruel). In our predominantly male veteran population, 82% of individuals with DE symptoms (dry eye questionnaire 6) reported one or more of these qualities when describing their eye symptoms [4]. The most common descriptors were “tiring-exhausting” (56%), “aching” (56%), and “hot burning” (53%) [4]. Using a modified version of the Neuropathic Pain Symptom Inventory [18] (NPSI-Eye), we found that both spontaneous and evoked pain were frequent complaints in our cohort with DE symptoms [4]. Specifically, patients frequently reported evoked pain to wind and light [19]. In 220 subjects with mild or greater DE symptoms, 161 individuals (73%) reported pain sensitivity to light, with 94 (43%) rating the sensitivity as moderate-severe (4 on scale of 0-10). Similarly, 137 (62%) reported pain sensitivity to wind, with 78 (35%) individuals rating the sensitivity as moderate-severe.

The epidemiology of ocular itch

The epidemiology of ocular itch is less well characterized. However, its prevalence is probably more frequent than previously believed. In fact, 118 of 400 (29.5%) patients seen in an outpatient eye clinic reported chronic ocular itch (defined as itch lasting > 6 weeks [20]). Like dry eye and ocular pain, ocular itch was more frequent in women. Chronic ocular itch was associated with many ocular surface diseases beyond allergic conjunctivitis, including dry eye (odd ratio (OR) 2.6; 95% CI, 1.7–4.1) and blepharitis (OR=2.0; 95% CI, 1.1–3.8) [21].

NOCICEPTIVE AND PRURICEPTIVE INNERVATION OF THE CORNEA

The cornea is innervated by the primary sensory neurons arising from the ophthalmic branch of the trigeminal nerve. Most of these fibers are unmyelinated C fibers with a few thinly myelinated A δ -fibers also present [22, 23]. Different nerve types respond to different environmental stimuli. A δ -mechanonociceptors (~20% of nerves) sense mechanical stimuli, polymodal C-nociceptors (PmC, ~70%) sense chemical, thermal and endogenous inflammatory mediators (although most are also mechanosensitive), and C-fiber cold thermoreceptors (~10%) sense reduction of temperature as seen with evaporation [22-25]. Specialized mechanically insensitive (chemo-) nociceptors (CMi) have also been suggested to exist in the cornea (and are present in most other tissues including the skin) [26-31]. Evidence in support of their existence in the cornea includes the detection of C-fibers that have a conduction velocity within the range of CMi and corneal receptiveness to chemicals such as histamine and bradykinin. In the skin, signaling in response to these mediators is almost exclusively transmitted by CMi-fibers [27-30]. Upon activation CMi-fibers also produce neurogenic inflammation to a much greater extent than PmC-fibers [30, 32].

In the skin CMi-fibers are indispensable for the transduction and transmission of histaminergic itch and play a role in neuronal sensitization and inflammation [32-35]. Histamine responsive CMi-fibers act as “selective” pruriceptors [28, 29]. They likely play a similar role in an ocular context. Unlike many types of acute itch, most chronic itch conditions of the skin do not respond to anti-histamines nor exhibit signs of CMi-fiber involvement, and hence itch-signaling is thought to occur via the non-histaminergic PmC-mediated pathway [10, 32, 36, 37]. PmC-fibers are not itch-“selective” and the neuronal

encoding that allow these afferents to act as both pruriceptive and nociceptive fibers under different conditions is a matter of ongoing contention [38, 39]. Currently, no treatments directly targeting itch and pain relevant transduction receptors on PmC-fibers are available (but several are under development [40, 41]).

SHARED MOLECULAR MECHANISMS BETWEEN OCULAR DRYNESS, PAIN, AND ITCH

Inflammation

Injury to epithelial cells and peripheral nerves causes the release of inflammatory mediators such as substance P, calcitonin gene-related peptide (CGRP), and neurokinin A. These mediators co-activate residing mast cells and macrophages and recruit additional immune system cells to the site of injury [31, 42, 43]. These cells subsequently release signaling mediators that directly activate or sensitize nociceptive and pruriceptive units, including bradykinin, prostaglandins, serotonin, glutamate, tryptase and histamine (the later two being particularly important in itch transmission) [29, 31, 34, 44-47].

Activated immune cells also release other inflammatory mediators such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 β [48]. This type of inflammatory milieu has been found to be an important component of chronic itch and DE, however it is unclear which aspects of the neurogenic and immunological response pattern determine whether pruriceptive or nociceptive signaling results [37-39]. In the skin, recruitment of T cells lead to the release of specific cytokines involved in itch, namely IL-2 and IL-31 [49-51]. Many inflammatory mediators, such as TNF α , IL1, IL6 [52, 53], PGE₂ [54], MMP-9 [55], have been found elevated in the tears of DE patients. T cells have also been detected more frequently in the conjunctivae of DE patients compared to controls[56].

Neuropeptides

Nerve growth factor (NGF) has been found elevated in the tears of DE patients and has been implicated in chronic itch [57]. NGF causes increased terminal nerve sprouting and reorganization of peptidergic nerves fibers, including pruriceptive fibers. NGF also induces expressional changes for transduction molecules, in C and A δ -fibers, resulting in an overall more excitable fiber phenotype [34, 44, 58]. In human skin, exogenous overexpression challenges of NGF lead to prolonged mechanical and heat hyperalgesia and increased itch in response to both histaminergic and non-histaminergic (cowhage) itch provocations [34, 58]. This most likely occurs through sensitization of primary nociceptive afferents. NGF has been found increased in atopic dermatitis skin, is associated with psoriatic itch and is closely linked to allergic inflammation through eosinophils, which both produce NGF themselves and release inflammatory mediators in response to NGF-binding [59, 60]. Release of CGRP from peptidergic C-fibers by retrograde signaling in terminal arborizations causes erythema and promotes migration of immune system cells to the damaged or irritated area [31, 34, 42]. Substance P, released in the same manner as CGRP has, beyond co-activating mast cells and promoting extravasation, a role in direct stimulation of PmC-nociceptors [31, 34, 42]. However, it is not clear whether NGF is beneficial or detrimental in DE. Autologous serum tears, a common treatment for recalcitrant DE, contain many growth factors including NGF;

its beneficial effects on symptoms and signs of disease is believed to be partially mediated by NGF [61, 62].

Ion channels

Prolonged neuropathic damage to nerves can cause complex reorganization of their expressional profile typically resulting in more excitable phenotypes and ectopic discharging. Mechanistically, this is largely prompted by the changes in ion channel expression [44, 63]. Different ion channels are found on the terminal nerve endings of corneal nerves, including members of the transient receptor protein (TRP) channel family. TRPV1 on PmC and CMi-neurons sense heat, chemicals, and abnormal pH [25] while TRMP8 on cold thermoreceptors sense cooling [64]. In addition, TRP-channels TRPV3 and 4 are expressed and involved in innocuous thermosensation under non-pathological condition [65]. Inflammation has been found not only to enhance the function of existing receptors (through phosphorylation) but also to induce expression and de novo transcription of additional channels [44, 63, 66]. Changes in the function of several other channels, including TRPA1, which is implicated in both pain and non-histaminergic pruriceptive signaling, voltage-gated sodium (Nav1.7-1.9), calcium, and potassium channels is a further downstream consequence [37, 41, 44, 63, 66, 67].

SHARED NEUROPHYSIOLOGICAL ABNORMALITIES BETWEEN OCULAR DRYNESS, PAIN, AND ITCH

Upregulation of various molecules (inflammatory mediators, NGF, TRP, other ion channels) as well as prolonged abrasive damage (manifesting as fluorescein staining) on the cornea leads to altered function of somatosensory nerves. Pain generated due to sensory nerve dysfunction (in the peripheral or central nervous system) is termed neuropathic pain [22-25].

Peripheral sensitization is defined as reduced threshold and/or increased responsiveness of peripheral nociceptive neurons in response to stimulation of their receptive fields [68]. Sensitized nerves demonstrate enhanced signaling (i.e. generation of an action potential) and conduction (i.e. propagation of the action potential) both through normal pathways as well as generation of ectopic action potential (i.e. in absence of any appropriate stimulus) [48]. Furthermore, signaling from nerves that are not nociceptive in nature, such as those that sense light touch, can converge onto nociceptive spinal dorsal horn pathways after a sufficient tissue injury, and thus give rise to pain perception (allodynia) [34, 38, 69], see Fig. 1.

Many insults, such as surgery, air pollution, inflammation, and perhaps prolonged abrasive damage can injure peripheral corneal nerves. In fact, in vivo confocal microscopy has demonstrated corneal nerve alterations in the setting of corneal surgery [70] and Sjögren's syndrome (a condition in which chronic corneal staining is a hallmark) [71]. Electrophysiologically, peripheral corneal nerves have been found to sensitize when subjected to an inflammatory milieu and after lacrimal gland transection [72, 73]. Nerve damage, increased afferent traffic through peripheral nerves, and persistent inflammation can cause central sensitization (e.g. maladaptive neuroplasticity of the central nervous system)

[34, 44, 74] with enhancement of excitatory neurons and blocking of inhibitory neurons occurring on a central level [69]. With central sensitization and as seen in DE, symptoms of disease are often not related to peripheral findings [1, 2, 75].

After leaving the cornea, peripheral corneal nerves synapse with second-order neurons in the Vi/Vc and Vc/C₁ regions within the trigeminal nucleus caudalis. In animal models of uveitis and photokeratitis, evidence of central sensitization was demonstrated as ocular neurons in the Vc/C₁ region became more sensitive to ocular stimuli [76, 77] and had increased convergent input from periocular skin [76]. In a rat model of tear deficiency after lacrimal gland removal, neurons in both the Vi/Vc and Vc/C₁ regions were more responsive to ocular stimuli with hypertonic saline and had increased convergent input was found from periocular skin [78]. Such central sensitization processes can explain DE symptoms such as pain in response to natural stimuli such as wind (i.e. hyperalgesia), by non-nociceptive fibers converging onto nociceptive second order neurons [34, 38, 44]. Notably, neuronal sensitization signs for pain, hyperalgesia and allodynia, are closely paralleled by signs of neuronal sensitization for itch conditions, i.e. *alloknesis* (itch in response to innocuous tactile stimuli) and *hyperknesis* (increased itch in response to normally itchy/painful stimuli). This highlights the shared neurobiology of nociceptive and pruriceptive circuitries [33, 38, 79], see also Fig. 1.

Decreased inhibition is also a component of central sensitization and reduced conditioned pain modulation capability would thus be expected in painful DE, as has been shown in virtually all other painful conditions [80, 81]. Just as spinal transmission of pain and itch from dorsal root fibers is under GABAergic modulation, so is signaling from the trigeminal nerve [82, 83]. Microinjections with the GABA agonist muscimol into the Vi/Vc decreased nociceptive transmission (stimulated by delivering pulses of CO₂ to the ocular surface) at the Vc/C₁. Oppositely, GABAergic activation at the Vi/Vc facilitated transmission of at Vc/C₁, indicating disinhibition of descending inhibitory pathways. Notably, local injection of muscimol at recording sites (Vi/Vc and Vc/C₁) inhibited nociceptive transmission from all tested units [83]. In the context of itch, segmental spinal gating is well established and constitutes the mechanistic basis of scratch-induced itch relieve [37, 38, 84]. This inhibition is mediated basic helix-loop-helix-5-expressing interneurons, which receive convergent input from selective nociceptive units [37, 84]. However whether this inhibitory circuitry exists for ocular somatosensation has not yet been elucidated.

SHARED GENETIC SUSCEPTIBILITY TO OCULAR DRYNESS, PAIN, AND ITCH

DE has also been found to have a hereditary component [85] with genetic polymorphisms in pro-inflammatory genes (e.g. IL1 and IL6R) found to associate with DE in a Korean population [86]. DE and non-ocular pain have also been linked genetically with chronic widespread musculoskeletal pain, chronic pelvic pain, and irritable bowel syndrome and DE linked by 2 latent genetic factors [87]. Genome wide association studies in European [88] and Chinese [89] populations also found multiple loci associated with Sjögrens syndrome (SS). Interestingly, none of the genes encoded for salivary or lacrimal components but

instead were associated with immune activity and inflammation, such antibody production and clearance, cytokine production, and immune cell proliferation [88, 90]. Genetic susceptibility to itch *per se* has only been very sparsely studied although many dermatologic itch conditions have a significant hereditary component. Notably, Individuals with one of several well-characterized mutations in the filaggrin gene are strongly predisposed to development of itching conditions such as atopic dermatitis and dry skin [91, 92]. However, this is foremost associated with effects on skin barrier deficiency rather than on pruriceptive processing.

RESPONSE TO TREATMENTS

Treatments for DE symptoms target the ocular surface, focusing on various aspects of tear dysfunction. The most common class of topical medications used in DE is the anti-inflammatories, which include corticosteroids, cyclosporine, and lifitigrastr. Given the close relationship between inflammation and nociceptor sensitization, decreasing inflammation has the effect of also reducing sensations of pain and itch. However, some patients report persistent symptoms on current therapies [93]. Treatments that target nerve function may improve symptoms of dryness, ocular pain, and itch in those whose symptoms are partially neuropathic in origin (Table 1). While some therapies, such as autologous serum tears, have been found to improve symptoms of dryness and evoked pain to light [94], their effect on ocular itch are not known. We have anecdotally used gabapentin and pregabalin in several patients with symptoms of dryness and ocular pain not responsive to traditional therapies. We found an effect in most patients when these agents were used at relatively high doses (900-1200 mg 3 times daily for gabapentin; 150 mg 2 times a day for pregabalin). Gabapentinoids, and other anti-neuropathic pain medicines, have also been used to treat chronic itch suspected to rely on the non-histaminergic itch pathway suggesting common underlying mechanisms [82, 95, 96]. Data is lacking however, on which anti-itch treatments will be most effective for chronic ocular itch. Recently, significant headway has been made as to characterizing patients with painful peripheral neuropathies by their specific sensory phenotype and sensitization pattern [44, 63, 97-99]. This not only yields consistent patient subgroups within the same formal diagnoses, but has also been shown to predict treatment responses to various centrally and peripherally acting analgesics [98]. Adapted psychophysical testing for ocular and periocular structures might yield similar mechanistic and clinical advances in relation to DE associated pain and itch.

LIMITATIONS

Most studies of ocular itch have focused on allergic conjunctivitis in which histamine signaling plays a major role [100, 101]. However, it is known that most cases of chronic itch are not mediated by histamine and likely rely on a distinct neuronal pathway [36]. Studies are therefore needed to elucidate mechanisms of ocular itch including assessing whether inflammatory mediators found in chronic itch (e.g. IL-31) are also involved in ocular itch. Furthermore, data are needed on electrophysiological and molecular changes (TRP, voltage-gated channels) in humans and animal models of ocular itch.

CONCLUSIONS

In this review we outlined shared features between symptoms of ocular dryness, pain, and itch, suggesting that all 3 sensations are mediated by shared underlying mechanisms, namely nerve sensitization in peripheral and central nerves. More research is needed on studying the epidemiology of ocular sensations in different populations, sensory phenotypes, molecular mechanisms and electrophysiological changes in animal models, and response to therapeutics therapies, whether topical or systemic, that will allow improved and individualized treatment in this patient population.

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Key points

- This review highlights the most recent research into epidemiology, pathophysiology and management of sensory symptoms of dryness, pain and itch from the ocular surface
- Chronic ocular dryness, pain, and itch are prevalent complaints which correlate poorly with ocular surface findings and are difficult to adequately treat
- Shared features between chronic ocular surface dysesthesias and non-ocular neuropathic pain conditions point are evident
- Recent studies suggests that in addition to neuromorphological aberrations, peripheral and central neuronal sensitization is involved in generating and maintaining chronic ocular sensory symptoms
- Future basic and clinical studies focusing on the neurobiology of ocular pain and itch sensitization are needed

Figure 1.

Diagram showing potential parallel and shared pathways between the ocular sensations of itch, pain, and dryness as well as analogue mechanisms for development of sensory dysesthesias. After injury or excessive dryness, ocular surface epithelial cells secrete a variety of inflammatory mediators (e.g. prostaglandin E₂ (PGE₂), serotonin, adenosine triphosphate (ATP) and protons that activate peripheral peptidergic C-fibers. These fibers in turn secrete neuropeptides (CGRP and Substance P), which are conducive to eliciting an inflammatory response in the area. Inflammatory cells secrete various cytokines (tumor necrosis factor α (TNF α) and interleukin-1 β (IL-1 β), among others), which alter the ocular surface environment (e.g. increased osmolarity) thus contributing to rekindling the cascade.

The release of pro-inflammatory mediators and the ocular surface alterations contribute to peripheral afferent sensitization (bottom lightning bolt) with increased responsiveness to external stimuli and spontaneous activation of the primary nociceptive and pruriceptive afferents. It is unclear which specific inflammatory or neuropathic preconditions result in distinct sensory perception of itch and pain (or both occurring simultaneously). However, certain mediators, such as histamine appear to shift signaling towards pruriception, while e.g. bradykinin mediates predominantly pain. Moreover, certain conditions are more consistently associated with pain, e.g. DE, while others are more commonly associated with itch, e.g. allergic conjunctivitis. Persistent peripheral barrage leads to amplified central nervous system processing (i.e. central sensitization) including augmented excitatory (top lightning bolts) and decreased descending as well as segmental inhibitory transmission (not shown). A previously proposed model suggests that pruriceptive and nociceptive afferents selectively sensitize (top lightning bolts) facilitatory interneurons that also receive input from low-threshold thermoreceptor, mechanoreceptors or even convergent input from the retina. Following such sensitization, nociceptive or pruriceptive 2nd order neurons exhibit enhanced responses to normally innocuous stimuli resulting in allodynia for pain and allodynia for itch. The precise neural circuitry underlying such dysesthesias evoked by pain and itch remains unclear, particularly in the context of ocular pain and itch.

Table 1

Similarities between sensations of chronic itch, pain, and dryness.

	Similarities between chronic itch, pain, and DE	Itch specific
Symptoms	Unpleasant, source of morbidity, negatively impact quality of life. Sensations often co-exist.	Itch elicits scratching while pain elicits withdrawal
Inflammation	Induces and maintains sensitization	IL-31 and histamine more specific to itch
Other mediators	Nerve growth factor (NGF) involved	NGF causes moderately increased itch sensitivity to non-histaminergic (cowhage) provocations
Peripheral Transmission and Sensitization	Involve increased responsiveness and reduced threshold of peripheral nociceptive neurons, with changes in TRPV1/A1 function	PAR2 involved in non-histaminergic chronic itch.
Central disinhibition	Signaling from primary afferents are under gate-control in the spinal dorsal horn (nucleus caudalis for ocular structures)	Recently discovered BHLHB-5 interneurons mediate alleviation by homotopic stimulation. Impairment of such gating would blunt scratch/rubbing relieve
Central Transmission and Sensitization	Involve increased CNS excitatory and decreased inhibitory signal transmission.	Gastrin-releasing peptide receptor expressing neurons essential for itch transmission. Imbalance between μ - and κ -opioids receptors in chronic itch.
Higher order processing	Multiple brain areas involved, both sensory and affective. Sensations are not a direct measure of input. All associated with co-morbidities that affect higher order pain processing, such as depression and anxiety	Precuneus involved in itch. The striatum and midbrain reward areas are associated with scratch-evoked pleasantness
Treatment	Respond in some degree to neuropathic pain medication	Anti-IL-4, IL-13, and IL-31, butorphanol (κ -opioid agonist) have shown success in chronic itch

BHLHB5 = basic helix-loop-helix member 5; CNS = central nervous system; DE = dry eye; IL=interleukin; GRP = Gastrin-releasing peptide; NGF = nerve growth factor; PAR2 = Proteinase-activated receptor 2; TRP = Transient receptor potential channels