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Patients with more severe symptoms of neuropathic ocular pain report more frequent and severe chronic overlapping pain conditions and psychiatric disease

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Abstract

Objective—To study chronic pain and mental health profiles in patients with dry eye (DE) symptoms, comparing those with high and low levels of neuropathic ocular pain (NOP) complaints.

Design—Cross-sectional study of 181 patients with DE symptoms (dry eye questionnaire score ≥6) seen in the Miami Veterans Affairs eye clinic. An evaluation was performed consisting of questionnaires regarding DE symptoms, NOP complaints (burning, sensitivity to wind, light and cold/hot temperatures) and pain elsewhere in the body (non-ocular). This was followed by a comprehensive ocular surface examination. The patients' comorbidities, medications, mental health (depression and post-traumatic stress disorder) and quality-of-life indices were also obtained. Patients were classified using cluster analysis into either the 'high NOP' or 'low NOP'

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group. Subsequent analyses were performed to examine differences in ocular and non-ocular parameters between these two groups.

Results—Despite similar ocular surface findings, patients in the high NOP group had very different systemic (non-ocular) profiles with higher overall pain intensity ratings, higher frequency of comorbid chronic centralised pain conditions, lower quality-of-life indices and more abnormal mental health scores than those in the low NOP group.

Conclusions—Consistent with a chronic overlapping pain condition, patients with DE disease with more severe NOP symptoms report more frequent and severe non-ocular functional comorbid pain disorders.

INTRODUCTION

Dry eye disease (DED) represents a heterogeneous and multifactorial group of disorders that affects the tears and ocular surface and results in discomfort and unpleasant visual phenomena, and in some cases, damage to the ocular surface.[1] In the USA, it is estimated that DED has a prevalence of 15% in the general population, with prevalence estimates ranging from 5% to 30% in patients aged ≥50 worldwide.[2] The morbidity of DED is high and its symptoms are a leading cause of visits to ophthalmologists and optometrists. DED is generally classified based on its presumed aetiology, including aqueous deficiency and evaporative dry eye (DE).[1] Treatment options are often chosen on the basis of these presumed ocular abnormalities despite the fact that previous literature indicates that objective ocular physical findings do not correlate well with DE symptoms.[3–5]

The discrepancy between symptoms and signs of disease may be partially explained by another, less-well-studied, component of DE, namely the presence of neuropathic ocular pain (NOP). Neuropathic pain represents pathological neuroplasticity of the somatosensory system associated with spontaneous firing of peripheral neurones (peripheral sensitisation) and/or higher sensory neurones (central sensitisation).[6] Many events including tear hyperosmolarity, air pollution, low humidity and surgery can stress and injure corneal nerves and trigger maladaptive neuroplasticity in vulnerable patients, leading to the development of NOP.[7,8] While no diagnostic tests are currently available to definitively diagnose NOP, there are several findings that suggest its presence in some patients with DED. For example, symptoms in some patients with DED mirror those found in non-ocular neuropathic pain disorders including spontaneous burning pain, hyperalgesia and allodynia (which in the eye manifest as wind-evoked and light-evoked pain).[8,9] Furthermore, patients with these symptoms have a more severe and chronic DE course[9] and have a less favourable response to artificial tears,[10] suggesting that these descriptors may be useful in identifying a subtype of DED that may result from somatosensory dysfunction and produce a chronic phenotype.

The phenomenon of a ‘chronic pain condition’ is somewhat poorly defined, but is essentially considered to be the persistence of pain past the point where resolution might reasonably be expected (often defined as ≥6 months). It is now understood that many individuals suffering from one form of chronic pain often have other chronic pain conditions, sometimes referred to as chronic overlapping pain conditions (COPCs).[11] Central sensitisation has been postulated to underlie some frequently coexistent functional pain conditions (including

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fibromyalgia, irritable bowel syndrome and temporomandibular pain),[1213] and when these processes encompass both functional and structural chronic pain conditions (eg, diabetic neuropathy, osteoarthritis and low back pain), this phenomenon has been termed central sensitivity syndrome (CSS).[14] DED and other COPC are also associated with other comorbidities including mood disorders, sleep abnormalities and decreased quality of life.[15–18] As such, we hypothesised that in select cases patients with features suggestive of NOP may describe DE symptoms as a peripheral manifestation of a CSS. In further support of our hypothesis, central pain disorders can be associated with altered pain processing and this has been demonstrated in some patients with DED both as altered corneal[19–22] and forearm sensitivity.[23]

We previously demonstrated that DE symptom severity correlated with severity of pain elsewhere in the body (non-ocular), depression and post-traumatic stress disease (PTSD) more strongly than it did with ocular surface parameters.[24] Taking this idea a step further, in this paper, we test our hypothesis by classifying patients with DE symptoms into groups based on complaints suggestive of NOP. We then compared features of CSS (pain ratings, comorbid pain conditions and mental health indices) between these groups. We hypothesised that patients with more severe complaints suggestive of NOP would have higher ocular and non-ocular pain ratings, more frequent COPCs and higher depression and PTSD scores compared with those with less severe NOP complaints.

METHODS

Study population

Patients were prospectively recruited from the Miami Veterans Affairs (VA) Healthcare System eye clinic from October 2013 to July 2015, after Miami VA Institutional Review Board approval, and informed consent was obtained from all participants. Patients with mild or greater DE symptoms (defined as dry eye questionnaire 5 (DEQ5) score of ≥6) and otherwise healthy eyelid and corneal anatomy were included. To study patients with ‘idiopathic’ DE symptoms, we excluded patients with conditions known to underlie DE symptoms including infection, contact lens use, history of refractive, glaucoma or retina surgery, cataract surgery within the preceding 6 months, any use of ocular medications other than artificial tears (eg, glaucoma medication), medical history of HIV, sarcoidosis, graft-versus-host disease or collagen vascular diseases. The study was conducted in accordance with the principles of the Declaration of Helsinki and complied with the requirements of the United States Health Insurance Portability and Accountability Act.

Data collected

For each individual, demographic information, past ocular and medical history and medication information were collected.

Dry eye symptoms—Patients completed the DEQ5.[25] The DEQ5 is a validated, five-item questionnaire that combines patient responses regarding ‘eye discomfort’ (frequency and intensity), ‘eye dryness’ (frequency and intensity) and ‘watery eyes’ (frequency) during the past month. DEQ5 scores can range from 0 to 22, with higher scores indicating greater

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severity of symptoms. A cut-off of ≥6 was used to define a population of patients with mild or greater DE symptoms.[25] The ocular surface disease index (OSDI)[26] was also administered and scored on a 0–100 scale, with higher scores indicating greater disability associated with DE symptoms.

NOP complaints—Based on our prior data,[24] features suggestive of NOP were assessed using four questions: (1) presence of spontaneous burning ocular pain, presence of evoked pain, including ocular pain caused or increased by (2) wind, (3) light and (4) air temperature (air conditioned/warm weather), with all responses rated on a scale from 0 to 10. Using a two-step cluster analysis based on burning, sensitivity to light, wind and temperature, the patient population was divided into two groups that were significantly different from each other regarding these NOP complaints and were subsequently termed ‘high NOP’ and ‘low NOP’ groups. The remaining analyses were performed evaluating for differences in parameters between these cluster groups.

Ocular surface evaluation—All patients underwent tear film assessment, including measurement of (1) tear osmolarity (TearLAB, San Diego, California, USA) (once in each eye); (2) tear breakup time (5 μL fluorescein placed, three measurements taken in each eye and averaged); (3) corneal epithelial cell disruption measured via corneal staining (National Eye Institute) scale,[27] five areas of cornea assessed with a score of 0–3 in each, total 15; (4) tear production measured via Schirmer’s strips with anaesthesia; and (5) meibomian gland assessment. Eyelid vascularity was graded on a scale of 0–3 (0=none; 1=mild engorgement; 2=moderate engorgement; 3=severe engorgement, based on photographs) and meibum quality on a scale of 0–4 (0=clear; 1=cloudy; 2=granular; 3=toothpaste; 4=no meibum extracted).[28]

Non-ocular pain phenotypes—Patients were asked about the presence of several chronic pain conditions (>3 months in duration). These included primary (functional) forms of central sensitisation[12] such as headaches, trigeminal neuralgia, temporomandibular joint pain, fibromyalgia, migraines, tendonitis, abdominal pain, pelvic pain, back pain, muscle pain and central pain syndrome, as well as secondary (structural) conditions[12] such as arthritis, chronic postsurgical pain, diabetic neuropathy, sciatica, burn pain, post-herpetic neuralgia and cancer pain. Complex regional pain syndrome/causalgia was considered an individual CSS.[12]

Pain drawing—Patients were asked to mark all current locations of pain on a front and back silhouette of the human body. The number of locations marked was added to obtain the total number of current pain locations.

Non-ocular pain severity—A numerical rating scale questionnaire for concurrent non-ocular pain was used (“How would you describe the overall intensity of your pain, *on average* during the last week?” and “How would you describe the overall intensity of your pain, *at its worst* during the last week?” Scale: 0–10 for each question).

Mental health and quality-of-life indices—Symptoms of PTSD were assessed via the PTSD checklist—military version (score 17–85)[29] and symptoms of depression via the

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patient health questionnaire 9 (score 0–27).[30] The short-form health survey—physical and mental health composite scores (score 0–100, 0 indicates the lowest level of health and 100 the highest level of health) were used to assess quality-of-life indices.

Statistical analysis

Data were entered into a standardised database. Statistical analyses were performed using SPSS V.22.0 (SPSS, Chicago, Illinois, USA) statistical package. Student's t test, Mann–Whitney U, χ^2 and Fisher's exact tests were used, as appropriate, to compare variables of interest between the two DE symptom groups.

RESULTS

Demographics and comorbidities by DE subgroup

In total, 181 veterans with DE symptoms (DEQ5≥6) participated in the study (mean age 64 years, 91% men). Full demographic characteristics of the study sample, grouped by features suggestive of NOP, are presented in table 1. The low NOP group consisted of 130 patients with significantly less features suggestive of NOP (burning score 2.3±2.7, sensitivity to wind 1.3±1.9, light 2.0±2.2, temperature 1.1±1.8) compared with the high NOP group (n=51; burning score 6.3±2.5, sensitivity to wind 7.2±2.1, light 7.6±2.2, temperature 5.4±3.4). These groups had comparable demographics with a large male majority. Comorbidities were likewise similar between groups with the exception of diabetes mellitus, which was more frequent in the low NOP group (40%) compared with the high NOP group (18%, p=0.004). Medication profiles, on the other hand, were different between the groups. Patients in the high NOP group were more frequently using anxiolytics (69%), antidepressants (59%) and analgesics (78%) compared with the low NOP group (30%, 38% and 57%, respectively; p value <0.05 for all).

DE symptoms and ocular surface signs by DE subgroup

No differences were seen in ocular surface parameters between the groups, including measurements of tear production, evaporation and corneal epithelial disruption (table 2). On the other hand, DE symptoms, as assessed by the DEQ5 and OSDI, were greater in the high versus low NOP group.

Systemic profiles by DE subgroup

Evaluating patients' non-ocular complaints, individuals in the high NOP group rated the average intensity of pain elsewhere in the body (non-ocular) significantly higher than the low NOP group (7.3±1.5 vs 4.3±2.7, respectively) (table 3). The high NOP group also had a higher frequency of primary (functional) centralised pain conditions than the low NOP group. Consistent with our hypothesis, mental health indices and quality-of-life metrics were also more abnormal in the high versus low NOP group (table 4).

CONCLUSION

The current study aimed to compare pain and health profiles in two groups of patients with DE symptoms, those with high versus low NOP complaints. We found that despite similar

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ocular surface findings, patients in the high NOP group had a very different systemic (non-ocular) profile, with higher overall ratings of pain intensity, greater frequency of primary (functional) centralised pain conditions and more abnormal mental health scores than patients with DE symptoms in the low NOP group. Our study extends the DED literature by demonstrating that patients with features suggestive of NOP not only have a more severe ocular pain profile,[9] but also have a more severe non-ocular pain profile, suggesting that these neuropathic pain-like symptoms may be useful in identifying patients whose DE symptoms likely represent a COPC.[1331–33]

DE symptoms likely occur as the end result of a number of pathological factors. Primary afferents can be stimulated by tear film abnormalities, such as hyperosmolarity and rapid evaporation, as well as by ocular surface inflammation, which is a well-described component of DED.[34] However, when considered in the context of chronic comorbid centralised pain syndromes, localised ocular surface changes alone are insufficient to explain all forms of DED pathology as it is well known that symptoms and signs of this disorder do not correlate.[5] Furthermore, patients with DE symptoms, as a group, have been found to have lower pain thresholds and pain tolerance in a site remote from the eye (ie, forearm) compared with controls, indicating central hypersensitivity.[23] Furthermore, our study findings are similar to that of a female twin cohort where DED was closely associated with a number of comorbid functional disorders, similar to those identified in our study.[35] This suggests that shared mechanisms underlying somatosensory dysfunction may account for the coexistence of comorbid conditions despite very different demographics in our independent cohorts.[33] Consistent with the biopsychosocial model of chronic pain, it is not surprising that those with more severe NOP complaints also had less healthy mental health indices.

The frequent observation of COPC in some patients has suggested that there may be shared genetic bases for these disorders.[313336] The role of genetics in the clinical variations seen in pain perception, processing and response to therapies has become increasingly more accepted.[637–39] Twin-based studies have been very instructive regarding the possible shared underlying mechanisms for DE and other COPC including chronic widespread pain, chronic pelvic pain, irritable bowel syndrome and psychiatric disease.[313340] Two latent factors with strong heritability were postulated as causal in a large female twin cohort, providing a possible link between DED and these other COPCs.[3336] Another genetic study evaluating a Korean non-Sjogren's DED population found an association between functional DNA polymorphisms in interleukin (IL)-1 and IL-6 receptor with DE symptoms.[41] Similarly, neuroinflammatory processes have been implicated in the pathophysiology of other neuropathic pain conditions.[42–44] These findings suggest that abnormal systemic inflammatory responses may underlie NOP and perhaps other COPC manifestations at varying sites via a mechanism that involves pro-inflammatory cytokines leading to sensitisation in various somatosensory pathways. This hypothesis will need to be tested in future studies.

As with all studies, our study has limitations, which must be considered when interpreting the study results. The current study sample consisted of US veterans, the majority of whom are older males. Consequently, given the prevalence of fibromyalgia, pelvic pain and migraine are higher in females, our sample size was insufficient to test an association

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between DED and these conditions. Although this provides contrast to several other studies examining exclusively female patients with DED, its results may not be generalised to other populations. It is encouraging, however, that our findings are similar to that of a British female cohort.[3536] Another possible limitation is that all measurements were taken on one day. Many factors can influence both subjective and objective measurements, and the retest reliability is not known. Finally, several techniques are emerging, which may be more accurate in evaluation of tear film parameters, including meniscometry, optical coherence tomography[45] and interferometry.[46] The use of these technologies may have resulted in different outcomes regarding the associations between DE symptoms and the measured parameters.

Despite these limitations, this study significantly extends the literature with novel findings demonstrating that a subset of patients with DED with symptoms suggestive of NOP report more comorbid centralised pain conditions. Significant comorbidities among patients with NOP suggest that there are likely to be significant repercussions on the health and well-being of these patients with DED. Further efforts to determine the underlying shared genetic factors in DED with other COPC may not only aid in better diagnosis and treatment of forms of DED, but is likely to be relevant to these other comorbid conditions.

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Table 1

Demographics and comorbidities of the study population

	Low NOP group* (n=130)	High NOP group* (n=51)	p Value
Demographics			
Age, mean (SD)	65 (11)	61 (11)	0.03
Gender, male, n (%)	121 (93%)	44 (86%)	0.15
Race, white, n (%)	67 (52%)	24 (47%)	0.44
Ethnicity, Hispanic, n (%)	36 (28%)	14 (28%)	0.97
Comorbidities			
Hypertension, n (%)	102 (79%)	34 (67%)	0.10
Diabetes mellitus, n (%)	52 (40%)	9 (18%)	0.004
Sleep apnoea, n (%)	28 (22%)	14 (28%)	0.40
BPH, n (%)	24 (19%)	8 (16%)	0.66
Medications			
Anxiolytic, n (%)	39 (30%)	35 (69%)	<0.0005
Antidepressant, n (%)	49 (38%)	30 (59%)	0.01
Antihistamine, n (%)	19 (15%)	13 (26%)	0.08
Analgesics, n (%)	74 (57%)	40 (78%)	0.007

* Determined by cluster analysis.

BPH, benign prostatic hypertrophy; n, number in each group; NOP, neuropathic ocular pain.

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Table 2

Dry eye symptoms and ocular surface examination in study population

	Low NOP group* (n=130) Mean (SD)	High NOP group* (n=51) Mean (SD)	p Value
Dry eye symptoms			
DEQ5 (range 0–22)	11.8 (3.5)	15.5 (3.2)	<0.0005
OSDI (range 0–100)	30 (20)	60 (20)	<0.0005
Ocular surface findings			
Tear osmolarity, mOsm/L	302 (16)	310 (18)	0.38
Tear film breakup time, s (faster time indicates more rapid tear evaporation)	9.2 (3.6)	8.9 (4.2)	0.69
Corneal staining, (0–15) (higher value indicates more surface disruption)	2.2 (2.8)	2.2 (2.3)	0.55
Schirmer's test, mm of moisture (lower value indicates lower tear production)	13.5 (6.1)	14.0 (7.2)	0.09
Eyelid vascularity, (0–3) (higher value indicates more abnormal vascularity)	0.68 (0.77)	0.60 (0.76)	0.82
Meibum quality (0–4) (higher value indicates more abnormal meibum)	1.8 (1.3)	2.0 (1.2)	0.48

All numbers represent the more severe value in either eye.

*Determined by cluster analysis.

DEQ5, dry eye questionnaire 5; NOP, neuropathic ocular pain; OSDI, ocular surface disease index.

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Table 3

Pain elsewhere in the body (non-ocular) in study population

	Low NOP group* (n=130)	High NOP group* (n=51)	p Value
Non-ocular pain intensity, averaged over past week (0–10), mean (SD)	4.3 (2.7)	7.3 (1.5)	<0.0005
Non-ocular pain intensity, worst during past week (0–10), mean (SD)	5.2 (3.2)	7.3 (1.5)	<0.0005
Number of chronic pain conditions, mean (SD)	4.2 (3.0)	5.9 (3.3)	0.002
Number of pain locations (by pain drawing), mean (SD)	2.6 (1.6)	3.3 (1.5)	0.009
Pain conditions†			
Primary central sensitisation			
Back pain	88 (68%)	46 (90%)	0.002
Muscle pain	57 (44%)	37 (73%)	0.001
Headaches	56 (43%)	29 (57%)	0.095
Tendonitis	33 (28%)	17 (37%)	0.290
Central pain syndrome	9 (7%)	10 (20%)	0.012
Trigeminal neuralgia	5 (4%)	7 (14%)	0.016
TMJ pain	5 (4%)	5 (10%)	0.115
Fibromyalgia	4 (3%)	0 (0%)	0.205
Migraines	5 (4%)	3 (6%)	0.549
Pelvic pain	2 (1.5%)	0 (0%)	0.373
Abdominal pain	1 (0.8%)	1 (2%)	0.490
Secondary central sensitisation			
Arthritis	76 (59%)	36 (71%)	0.131
Chronic postsurgical pain	28 (22%)	16 (31%)	0.165
Diabetic neuropathy	29 (22%)	10 (20%)	0.691
Sciatica	33 (25%)	18 (35%)	0.182
Burn pain	20 (15%)	14 (28%)	0.062
Postherpetic neuralgia	12 (9%)	6 (12%)	0.608
Cancer pain	12 (9%)	3 (6%)	0.462
Individual central sensitivity syndrome			
CRPS/causalgia	7 (5%)	8 (16%)	0.024

*Determined by cluster analysis.

†Classification from Yunus.[14]

CRPS, complex regional pain syndrome; NOP, neuropathic ocular pain; TMJ, temporomandibular joint pain.

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Table 4

Psychiatric complaints and quality of life in population sample

	Low NOP group* (n=130) Mean (SD)	High NOP group* (n=51) Mean (SD)	p Value
PTSD checklist—military version (17–85)	36 (17)	53 (21)	<0.0005
Depression score via PHQ9 (0–27)	7.6 (7.2)	13.5 (8.1)	<0.0005
SF-12, physical composite score (0–100)	41 (12)	34 (10)	0.001
SF-12, mental composite score (0–100)	47 (13)	41 (14)	0.005

*Determined by cluster analysis.

NOP, neuropathic ocular pain; PHQ9, patient health questionnaire 9; PTSD, post-traumatic stress disease; SF-12, short-form health survey questionnaire.