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Neuropathic Ocular Pain due to Dry Eye Is Associated With Multiple Comorbid Chronic Pain Syndromes

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Abstract: **Recent data show that dry eye (DE) susceptibility and other chronic pain syndromes (CPS) such as chronic widespread pain, irritable bowel syndrome, and pelvic pain, might share common heritable factors. Previously, we showed that DE patients described more severe symptoms and tended to report features of neuropathic ocular pain (NOP). We hypothesized that patients with a greater number of CPS would have a different DE phenotype compared with those with fewer CPS. We recruited a cohort of 154 DE patients from the Miami Veterans Affairs Hospital and defined high and low CPS groups using cluster analysis. In addition to worse nonocular pain complaints and higher post-traumatic stress disorder and depression scores ($P < .01$), we found that the high CPS group reported more severe neuropathic type DE symptoms compared with the low CPS group, including worse ocular pain assessed via 3 different pain scales ($P < .05$), with similar objective corneal DE signs. To our knowledge, this was the first study to show that DE patients who manifest a greater number of comorbid CPS reported more severe DE symptoms and features of NOP. These findings provided further evidence that NOP might represent a central pain disorder, and that shared mechanistic factors might underlie vulnerability to some forms of DE and other comorbid CPS.**

Perspective: ***DE patients reported more frequent CPS (high CPS group) and reported worse DE symptoms and ocular and nonocular pain scores. The high CPS group reported symptoms of NOP that share causal genetic factors with comorbid CPS. These results imply that an NOP evaluation and treatment should be considered for DE patients.***

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Key words: *Dry eye symptoms, neuropathic pain, neuropathic ocular pain, allodynia, hyperalgesia, chronic pain, chronic overlapping pain syndromes, central pain syndromes, comorbid pain syndromes.*

According to the Institute of Medicine Report on chronic pain in America, chronic pain conditions affect at least 116 million US adults at a cost of $560 to $635 billion annually in direct medical treatment and lost productivity.[27] The Institute of Medicine report further concluded that, "Chronic pain has a distinct pathology, causing changes throughout the nervous system that often worsen over time." Individuals who suffer from one form of chronic pain often have other chronic pain conditions. These individuals will often describe mood disorders, disrupted sleep, decreased energy, difficulty concentrating, and report an overall decrease in their enjoyment of life.[17,43,45,56,62,64] The phenomenon of "chronic pain syndromes" (CPS) is somewhat poorly

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defined, but is essentially considered to be the persistence of pain past the point at which resolution might reasonably be expected (often defined as ≥6 months). Such syndromes are thought to include functional disorders such as fibromyalgia, irritable bowel syndrome, temporomandibular pain, complex regional pain syndrome and chronic pelvic pain, as well as structural conditions such as diabetic neuropathy, osteoarthritis, and cancer pain, among others.

Dry eye (DE) is a common disorder that affects the quality of life of millions worldwide.[58] DE is characterized by symptoms of ocular discomfort and visual disturbances, as well as variable signs including tear film and ocular surface disruption and inflammatory changes.[20,41] Damage or dysfunction in the corneal somatosensory pathway has also been postulated as a component of DE in some patients because of the high density and superficial location of the corneal nociceptors, which makes them vulnerable to repeated damage and injury.[2,21,24] Episodic or ongoing damage to corneal nerves might result in permanent alteration of neuronal function, including reduced activation thresholds and increased excitability.[22,23] The abnormal corneal nerve morphology and sensitivity described in some patients with DE symptoms is consistent with this mechanism.[3,6,51]

We previously reported that a subset of DE patients described their symptoms in terms consistent with neuropathic pain, including features of evoked pain to wind and temperature as well as increased sensitivity to light (photoallodynia or photophobia).[23] In addition to DE symptoms of a specific neuropathic quality, the symptoms described by these patients also tended to be more severe and persistent than those of their "traditional" DE counterparts.[23] Furthermore, these symptoms were reported in the absence of objective ocular surface defects, and were more closely aligned to nonocular or central neurologic mechanisms rather than to the presence of any ongoing peripheral pathology.[18]

Additional evidence that some forms of DE represent a central disorder comes from work that showed increased forearm sensitivity to heat pain during objective quantitative sensory testing in DE patients.[56,61] Similar to other CPS, DE is also strongly associated with depression, posttraumatic stress disorder, and sleep disruption.[17,19,36] Recent evidence suggests that somatic and structural comorbid CPS, including DE, might share common genetic mechanistic factors.[38,62] Collectively, these findings suggest that in at least some individuals, DE might actually represent a chronic neuropathic pain syndrome.

Because of these results, in this study we hypothesized that DE patients with a greater number of chronic comorbid structural and functional pain syndromes (high CPS group) would show a different phenotype than those with fewer comorbid conditions (low CPS group). To study this question, we used cluster analysis to divide our population of symptomatic DE patients into these 2 groups according to their pain complaints. We then evaluated whether the high CPS group of DE patients reported symptoms of neuropathic ocular pain compared with the low CPS group of DE patients.

Methods

Population Sample

A cohort of 154 patients with DE symptoms, and a Dry Eye Questionnaire 5 (DEQ5) score ≥6 and normal eyelid and corneal anatomy were prospectively recruited from the Miami Veterans Affairs Healthcare System eye clinic between October 2013 and March 2015 and underwent a complete ocular surface examination. Patients were excluded from participation if they wore contact lenses, had ever undergone refractive, retinal, or glaucoma surgery, or had undergone cataract surgery within the past 6 months, used ocular medications with the exception of artificial tears, had a history of HIV infection, sarcoidosis, graft versus host disease, a collagen vascular disease, or acute ocular process such as conjunctivitis, infection, and iritis. The Miami Veterans Affairs institutional review board approval was granted (number 3011.02) to allow the prospective evaluation of patients after informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki and Declaration of the World Medical Association.

Data Collection

For each individual, we collected data on demographic characteristics, ocular and medical history, and current medications.

Binary CPS Phenotype Determination

Patients were asked about the presence of the following chronic pain conditions, defined as any of the following for >3 months duration: arthritis, burn pain, headaches, diabetic neuropathy, tendonitis, central pain syndrome, muscle pain, complex regional pain syndrome and/or causalgia, back pain, cancer pain, trigeminal neuralgia, sciatica, shingles, surgical pain, temporomandibular pain, and fibromyalgia. Patients were also given a pain drawing in which they marked current locations of pain. The total number of pain locations was computed from these drawings as a summary score. Using a 2-step cluster analysis on the basis of number of reported chronic pain conditions and the pain locations summary score, the patient population was divided into 2 groups. Cluster group 1 (n = 57) had a lower number of CPS (mean = 2.5, SD = 1.5) and a lower number of current pain locations (mean = 1.1, SD = .7). Cluster group 2 (n = 97) had a higher number of CPS (mean = 6.2, SD = 3.5) and a higher number of current pain locations (mean = 3.8, SD = 1.1). The remaining analyses were performed to evaluate differences in DE status between these high and low CPS cluster groups.

Ocular Surface Evaluation

All patients underwent a tear film assessment which included, in the order performed: 1) tear osmolarity (TearLAB, San Diego, CA), 2) tear breakup time, 3) corneal staining, 4) Schirmer strips with anesthesia, and 5) meibomian gland assessment. Tear osmolarity testing was performed once in each eye before instillation of eye drops. The osmolarity handpiece was held over the