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REVIEW

Why the symptoms and objective signs of dry eye disease may not correlate

Charles W. McMonnies[a,b,*]

[a] *School of Optometry and Vision Science, Australia*
[b] *University of New South Wales, Kensington, 2052, Australia*

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Abstract Cases of dry eye disease involving a neuropathic basis for symptoms and a poor correlation between symptoms and objective signs of dry eye disease can be associated with unsatisfactory responses to treatments which are limited to attempts to restore lacrimal function unit deficiencies. This review examines a wider range of circumstances under which the same kind of poor correlation between signs, symptoms and treatment results can be found. Some cases of computer vision syndrome can present for examination at times when objective signs related to reported symptoms have dissipated. A thorough history should explain this type of presentation for which symptoms might otherwise appear to be unexplained. However, mental health disorders can also be the basis for apparently unexplained levels of symptoms of dry eye disease. Anxiety, depression, hypochondriasis, stress, sleep and mood disorders as well as neuroticism for example, may be associated with exacerbation of symptoms to degrees that are not consistent with the levels of tear homeostasis anomalies that are assessed. The conclusion is drawn that failure to consider mental health comorbidities may result in symptomatic patients being exposed to less successful attempts to remediate tear dysfunctions when, for example, the symptoms have a somatic basis. Appropriate screening and referral to a psychologist or psychiatrist may be the key to managing some patients whose symptoms do not correlate with objective evidence of dry eye disease.

Introduction

Ocular irritations such as dry eye symptoms are one of the most common complaints of patients presenting to eyecare practitioners.[1] A survey of 13,517 patients presenting for eye and vision examinations in Canada found that 28.7 %

* Correspondence to: School of Optometry and Vision Science, 77 Cliff Avenue, Northbridge, New South Wales, 2063, Australia.
E-mail address: c.mcmonnies@unsw.edu.au

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reported dry eye symptoms.[2] Interviews of residents in 5 rural villages and one regional town in Indonesia found 27.5% reporting dry eye symptoms occurring often or constantly.[3] Using a Delphi process to examine the problems associated with classifying signs and symptoms of dry eye (or ocular surface disease) according to the underlying mechanism, 18 items suggestive of 23 alternative diagnoses that share some signs and symptoms with dry eye disease were identified.[4] These findings support the recommendation that dry eye syndrome should be included in the differential diagnosis of all patients presenting with symptoms of ocular discomfort.[5] However, conditions other than a dry eye syndrome such as allergy, basement membrane disease, conjunctivochalasis and blepharitis can present with symptoms found in dry eye patients.[6] Thus, for some patients who report symptoms of dry eye, a diagnosis other than dry eye disease, or a diagnosis that is comorbid with dry eye disease may be appropriate. In the absence of comorbidity with dry eye disease, signs of ocular surface disease could be more or less absent in some patients who report dry eye symptoms. Even in comorbid cases, signs of dry eye disease may not correspond with the level of symptoms. An assumption that complaints of dry eyes are due to ocular surface disease alone in such cases, and a subsequent related treatment emphasis on anomalies within the lacrimal function unit, could be more or less unproductive.

Sullivan and coauthors did not find a consistent relationship between common signs and symptoms of dry eye disease[7] and the poor relation between dry eye tests and symptoms represents a quandary in dry eye clinical research and practice.[8] Predictors of symptoms being less than signs of dry eye disease include increased age, the presence of Sjogren's syndrome and graft-versus-host disease.[9] Predictors of symptoms being greater than signs of dry eye disease include, the presence of chronic pain syndrome, atopic diseases, a known allergy, the use of antihistamines, osteoarthritis, depression and the use of anti-depressants.[9] This review examines other circumstances under which dry eye symptoms do not correspond with objective signs of ocular surface disease. The number of possibly relevant publications (shown in parentheses) found from PubMed searches (16th February 2020) using the following terms were: 'Dry eye and depression' (1620); 'dry eye and anxiety' (617); 'dry eye and stress' (540); 'dry eye and mood' (488);' dry eye and neuropathy' (389); dry eye and sleep' (153); 'dry eye and somatic disorders' (33); 'dry eye and post-traumatic stress disorder '(12); dry eye and neuroticism' (7). Selection of those which were found to be the most relevant and representative of a balanced account of this topic, as well as selected reports referenced in those publications, were included in this review.

Environmental symptom provocations: computer vision syndromes and adverse atmospheric conditions

Computer vision syndrome can be identified in patients whose dry eye symptoms are specific to computer use. For example, high incomplete blink rates contribute to any form of dry eye but are a particular problem for computer and electronic device users,[10] especially when combined with low overall blink rates so that blink efficiency is very low.[11] Rather than dysfunction in other parts of the lacrimal functional unit, some patients may have normal tear functions except for inefficient blinking.[11] In these cases of normal range tear homeostasis, repair of signs of over-exposure such as a desiccated epithelium can be rapid so that evidence of inefficient blinking has dissipated at the time of an examination. These cases of symptoms being greater than signs could be classified as idiopathic except that a specific history of symptom prevalence during computer use (or reading) is a prominent feature and such syndromes are well known.[10,12–14] Alternatively, dry eye symptoms may only be significant under other adverse conditions such as a harsh environment involving challenges to normal range tear functions. These challenges could include air movement and/or high temperature and/or low humidity, for example.[15] Following exposure to more favourable environments, objective signs of dry eye may be marginal or absent at the time of an examination. Patient history is the most common first choice clinical tool[16] and may be the basis for accurate diagnosis in such cases, when the conditions under which the symptoms occur are identified.

Three types of ocular pain symptoms

Many dry eye patients report ocular pain[17] which can be nociceptive, neuropathic or psychogenic.[18] The sensory component of pain is described as a nociceptive physiological response which is the progenitor of the experience of pain.[19] About 10%–15% of corneal nociceptors are cold sensitive and able to detect tear temperature changes such as occur with tear evaporation[20] Abnormally high stimulation of these nociceptors might occur when lipid layer deficiencies and/or a thin tear layer,[21] result in more rapid evaporation and associated tear cooling. About 20% of nociceptors respond exclusively to mechanical stimuli[20] which might include friction sensations associated with blink-related lid wiper movements over a desiccated ocular surface such as occurs in areas of tear break up. However, about 70% of corneal nociceptors are polymodal and able to respond to mechanical, heat, and chemical stimuli such as hyperosmolarity.[20] For patients attending an eye clinic, mechanical detection and pain thresholds measured on the cornea were correlated with dry eye symptoms and ocular pain, suggesting increased corneal sensitivity in patients with more severe dry eye symptoms.[22] However, ocular signs of dry eye in these patients were found to correlate poorly and non-significantly with corneal mechanical detection and pain thresholds,[22] supporting the view that dry eye pain is not just a matter of nociception. It appears likely that conditions other than loss of tear homeostasis can contribute to dry eye symptoms and treatment limited to restoration of impaired tear homeostasis may be less successful in such cases. In medical practice, the prevalence of physical symptoms not conclusively explained by signs or other indication of an organic disease ranges from 4% to 20% depending on the population studied and the methods of examination used.[23] This review examines how symptoms associated with comorbid disorders can help explain why symptom levels may not correlate with objective signs of dry eye disease.

Symptoms involving neuropathic pain

Patients with neuropathic pain can experience sensations of dryness even when their tear functions appear to be normal and their symptoms appear to be unexplained.[24] Neuropathic pain arises from direct lesion or damage to the somatosensory system and profound alterations to the normal peripheral and central neural processing of afferent input.[25] For instance, corneal nerve damage leads to neurotrophic keratopathy with associated disruption of neural circuits[26] and symptoms such as burning, tingling or electric pain.[27] Corneal esthesiometry and/or in vivo confocal microscopy may be crucially important for appropriate diagnosis of a neuropathic basis for symptoms.[22,28] Esthesiometry may detect abnormal corneal thresholds and in vivo confocal microscopy may detect corneal sub-basal plexus nerve fibre changes in the form of abnormal fibre length and the presence of beading and neuromas.[29] However, in vivo confocal microscopy and esthesiometry are not routinely available in clinical settings[27] and for example, neuropathic symptoms may be diagnosed as having a basis in somatisation which is discussed below. Neuropathic dry eye symptoms are often associated with numerous comorbid pain conditions and/or evidence of central pain processing abnormalities as well as mental health conditions.[30] Patients with contributions to their symptoms from both neuropathic and tear dysfunction mechanisms might be the most confusing and difficult to help. There is no drug targeting neuropathic pain[31] but maintenance of optimum tear homeostasis and avoidance of harsh environments which challenge tear functions, may aid repair of any corneal nerve damage.

The role of mental health conditions in contributing to dry eye symptoms

Vehof and coauthors described predictors of symptoms being greater than signs of dry eye disease, including the presence of a chronic pain syndrome, osteoarthritis, atopic diseases, depression, and the use of anti-depressants.[9] Similarly, Galor and coauthors reported that for some patients, dry eye symptoms can align more closely to conditions such as non-ocular pain, depression and post-traumatic stress disorder rather than to tear film parameters.[32] As discussed above, rapid tear evaporation and associated increased cooling as well as increases in hyperosmolarity as the tear layer thins in a 'break up' area can provoke symptoms which are reduced by eye closure. Consequently, a patient's failure to detect any reduction in symptoms when they are asked to close their eyes is consistent with factors other than evaporative tear dysfunction being a cause of their symptoms and so allowing the possibility that symptoms and signs will not correspond.[33] For example, Szakats and coauthors found evidence that supported the role of health anxiety and associated depression and anxiety-related symptoms in explaining the lack of correlation between symptoms and objective signs of dry eye disease.[34] For instance, after comparing asymptomatic and dry eye symptomatic patients, the scores for depression and anxiety were significantly worse in the symptomatic group.[34]

The prevalence of mental health conditions as an indication of how often they might be comorbid with dry eye syndromes

For the general population in the Netherlands the prevalence of psychiatric disorders was 41% compared to reports of 48% in the United States and 35% in Canada.[35] A study of patients attending general practices in London England found that 14% of patients consulted for an illness that was judged to be largely or entirely psychiatric in nature.[36] For patients seen in primary care, Tiller reported about 25% had comorbid anxiety and depression.[37] The difference between the number of patients with mental health disorders and the number who seek help for them, is indicative of negative attitudes toward such conditions and associated adverse stereotypes both self-ascribed as well as practitioner-ascribed.[38] Given the around 28% prevalence of dry eye disease found in population studies,[2,3] the high prevalence of psychiatric disorders[35] is consistent with some dry eye symptomatic patients having a comorbid mental health condition which could be influencing the severity of their symptoms. Unsuspected mental health contributions to dry eye symptoms may help explain the poor correlation of symptoms with objective signs of dry eye. In medical practice, the prevalence of physical symptoms not conclusively explained by an organic disease ranges from 4% to 20%.[23] Although psychiatric disorders are prevalent, many patients with a psychiatric condition remain unidentified in primary care.[39] The same discrepancy may be relevant to the practices of ophthalmologists and optometrists.

Somatization, hypochondriasis and illness anxiety

Somatization is the tendency for psychological stress to manifest in the form of physical symptoms.[40] Somatization has become the current terminology for unexplained symptoms and includes patients becoming preoccupied with bodily symptoms.[41] Somatic symptoms may be manifestations of anxiety and depressive states without having any basis in organic pathology.[42] The finding of no basis in organic pathology might be better described as no apparent basis in organic pathology. Costa and McCrae describe three models for the complex relations between somatic complaints and disease symptoms.[43] The simplest model is that all symptom reports involve perceptions which accurately represent reality whereas hypochondriasis is an unfounded belief in one's ill health.[43] Thus the second (malingering/hypochondriac) model described by Costa and McCrae involves a patient with so many symptoms that it is impossible to believe that they all represent reality, especially as no objective basis can be found for them.[43] The third model describes a continuum between under-reporting of symptoms and hypochondriasis.[43] In a large sample of dry eye patients, greater symptoms compared with signs was highly associated with lower self-perceived health[9] and illness anxiety.[44]

At least 33% of somatic symptoms are unexplained and these symptoms are chronic or recurrent in 20%–25% of patients.[45] Unexplained or multiple somatic symptoms are strongly associated with coexisting depressive and anxi-

ety disorders.[45] Other predictors of psychiatric co-morbidity include stress, lower self-rated health and higher somatic symptom severity, as well as higher healthcare utilization, difficult patient encounters as perceived by the practitioner, and chronic medical disorders.[45] Referral to a psychiatrist can cause a patient to feel humiliated and stigmatized and so more likely to not proceed to a psychiatric consultation.[46]

Quality of life and dry eye syndromes

Dry eye disease is accompanied by negative health-related quality of life consequences[47] with a significant impact on the symptoms of depression.[48] Shigeyasu and coauthors reported a significant reduction in quality-of-life in Japanese dry eye patients[31] and, vision-related quality-of-life was found to be impaired in Chinese dry eye patients as well as being also correlated with anxiety and depression.[49] While the consequences of reduced quality of life in dry eye patients can include mood alterations, depression and anxiety,[50] similarly dry eye disease is prevalent in patients with depressive and anxiety disorders, especially for patients who are older, have longer duration of psychiatric disorder, and who use a selective serotonin reuptake inhibitor.[51]

Anxiety

Anxiety is a distressing subjective experience and the hallmark of diagnosable psychiatric disorders including generalized anxiety disorder, social anxiety, post-traumatic stress disorder, generalized anxiety disorder, and specific phobias such as panic disorders.[52] It is difficult to distinguish generalized anxiety disorder from normal stress reactions and from other mood (affective) disorders.[52] Anxiety may be the most prevalent psychiatric symptom in the general population having a combined lifetime prevalence of 28%, which is far more than that of depressive disorders.[52] Stressful life events may precipitate or exacerbate anxiety and depressive disorders.[53] Conversely. reductions in the levels of anxiety were associated with treatment related reductions in dry eye symptoms[54] so that successful treatment of anxiety and depressive disorders may be found to improve the success of the treatment of dry eye disease.[55] That possibility might be more likely when symptoms are disproportionately high compared to objective signs.

Depression

Depression is one of the leading causes of disability world-wide.[56] Despite a favourable response to treatment, depression remains largely undetected and untreated.[57] The prevalence of depression at ages above 65 is 10%–15% and it is more common among those with a physical disease.[57] There is no reason to believe that depression is a normal part of ageing and, apart from physical impairment, risk factors include social isolation and loneliness.[57] Major depressive disorders negatively affect how people feel including causing them to feel sad and to lose interest or pleasure in activities that they once enjoyed, to lose interest in eating, to have difficulty sleeping, to experience loss of energy and to feel worthless or guilty.[58] An association between depression and dry eye symptoms has been demonstrated[59] and patients who are clinically depressed may perceive dry eye symptoms as being more severe as a consequence of being depressed.[60] For patients attending a dry eye clinic, short tear break up times and visual blurring were found to be associated with symptoms of depression suggesting a causal relationship[61] associated with reduced quality of life. The effect of adequate treatment of depression on successful therapy for comorbid diseases has been demonstrated[55] and may be of benefit in the management of dry eye disease. Conversely, effective dry eye disease treatment could have a positive impact on the symptoms of depression and anxiety.[54] For example, changes in dry eye symptoms were found to correlate with changes in measures of depression.[54] Optimum patient management might require that treatment for dry eye is combined with treatment for depression and anxiety[55] because treatment of dry eye disease could help reduce depression symptoms, and effective management of depression could help alleviate symptoms of dry eye.[60] However, some anti-depressive and anti-anxiety medications such as a selective serotonin reuptake inhibitor, may exacerbate dry eye disease.[51]

The relationship between depression and anxiety

Depression and anxiety are more severe expressions of the same states that may be discerned in normal patients as transient consequences of stress.[53] Of patients seen in primary care, about 25% have comorbid anxiety and depression.[37] They are diagnostically dissociable with anxiety being a core feature of depression.[62] Both are associated with significant morbidity and mortality.[37] Patients with anxiety and/or depression are particularly likely to present with physical complaints rather than mental health symptoms.[37]

Stress

The concept of stress poses additional problems in the study of negative affect conditions.[53] For instance, because the concept of a stress response has clear affinities with anxiety[53] stress can predispose patients to psychological and behavioral consequences.[63] Stress may be acute, episodic acute, and chronic as well as physical and/or emotional. For instance, stress may be due to the pressures of time, and/or be anticipatory (foreboding) and/or be situational such as stress associated with encountering people.[64] Stress may be associated with reduced quality of life.[65] Post-traumatic stress disorder is a mental health condition that is triggered by a terrifying event (experienced or witnessed).[66] Symptoms may include flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event.[66] Dry eye disease is associated with post-traumatic stress disorder and is prevalent among male and female veterans for example.[67] That dry eye symptoms are accompanied by negative health-related quality of life consequences[47] suggests that, rather than being a consequence of stress, dry eye disease symptoms could also contribute to stress.

Sleep and mood disorders

Ayaki and coauthors reported that, compared to other patients attending eye clinics, the prevalence of sleep and mood disorders was significantly higher in patients with dry eye.[68] Loss of sleep quality in patients with dry eye disease is correlated with the severity of dry eye disease.[69] Difficulty sleeping is also associated with major depressive[58] and anxiety disorders.[70]

Neuroticism and symptoms

Neuroticism is a personality factor involving the propensity to experience emotional distress and to report poor stress coping.[71] Consequently, neuroticism is intimately linked to somatic complaints[43] with Ichinohe and coauthors finding a significant relationship between neuroticism and the symptoms of dry eye disease.[72] Retrospective symptom reports remain the primary means by which individuals describe their health[71] and there are large individual differences in retrospective physical symptom reports that reflect a host of factors beyond objective illness.[43,71] For example, gender and neuroticism have emerged as significant predictors of retrospective symptom reports and one proposed mechanism by which neuroticism is linked to symptom reporting is via heightened symptom perception.[43,71]

The influence of gender

Gender is a significant predictor of retrospective symptom reports[43,71] and women are disproportionately affected by dry eye disease, are diagnosed at a younger age, and experience more severe symptoms compared with men.[73] Compared to females, males were found to exhibit less negative pain responses when focusing on the sensory component of pain (that is, having an increased threshold and tolerance for pain)[74] There is a strong association between dry eye disease and autoimmune disorders, especially those that affect women at many times the rate for men.[73] Sex hormones may also affect tear homeostasis and for example, it is possible that oestrogen modulates inflammatory events in dry eye.[75] Gender differences for dry eye disease become more apparent as age increases.[74] For Dutch people, women had a higher prevalence of mood and anxiety disorders than men[35] and a study of medical health care utilization in Germany found that significantly more women than men suffer from somatic complaints.[76] Accordingly, women report more intense, more numerous, and more frequent bodily symptoms than men including those which are medically unexplained.[77] For example, the finding of an excess of minor physical morbidity reported by women compared to men has been widely confirmed in representative community population studies in North America and Europe.[76] That finding was found to possibly be explained by factors such as lower social class status, high levels of chronic distress and poor perceived/self-assessed health.[76] That significantly higher symptom scores are reported by women in association with the finding of a lower correlation between symptoms and signs,[78] is consistent with some mental health disorders such as anxiety and mood disorders being more prevalent in women.[79]

Management of patients whose symptoms might have a basis in a mental health disorder

Again, that some dry eye symptoms might be related to a mental health disorder is consistent with the findings that at least 33% of somatic symptoms in primary care practices are unexplained, that these symptoms are chronic or recurrent in 20%–25% of patients and that unexplained or multiple somatic symptoms are strongly associated with coexisting depressive and anxiety disorders.[45] Other predictors of psychiatric co-morbidity include stress, lower self-rated health and higher somatic symptom severity, as well as higher healthcare utilization, difficult patient encounters as perceived by the practitioner, and chronic medical disorders.[45] These findings underline the possibility that the symptoms of some dry eye patients might be associated with mental health disorders. Depression and anxiety are the most likely comorbidities. The General Health Questionnaire is a 60-item self-administered instrument used for aiding the primary care practitioner in detecting those patients most likely to have psychiatric disorders such as depression and anxiety.[80] Such a long screening process appears likely to be inappropriate for the management of dry eye patients in most clinical circumstances. Lavigne and coauthors point out that while screening efficiency can be achieved by the use of brief screening measures, the overall screening process will be improved by paying attention to managing the large number of false positive cases.[81] The 14-item Hospital Anxiety and Depression Scale is used to screen for the contribution of mood disorder, especially depression and anxiety, in order to understand the significance of clinically reported symptoms.[82] It has been confirmed to be valid for use in primary-care practice.[82] Ideally, a patient would recognise that they need referral for assessment of their mental health[83] but that may be an unlikely prospect for the majority of patients who present with dry eye symptoms. The level of satisfaction with referrals of dry eye patients for psychiatrists depended on the quantity and quality of information provided by the referring primary-care practitioner.[83] Essential information would be that the patient's clinically significant dry eye symptoms do not correlate with objective evidence of dry eye disease as well as the results of screening instruments used. Primary-care practitioners can be less satisfied with mental health referrals made to psychiatrists, psychologists and social workers compared with referrals to other medical specialties.[83] Killaspy and coauthors found important deficits in communication from psychiatrists to the referring practitioner, especially in regard to non-attendees whose non-attendance may be the result of stigmatization associated with being referred to a psychiatrist.[84]

Summary

Symptoms of ocular discomfort which are typical of dry eye disease often persist despite appropriate local therapy, and cause continuing frustration for both patient and physician.[34] Apart from the level of reduced quality of life

associated with chronic symptoms, moderate to severe dry eye patients often become frustrated with their treatment course such as lack of success and the need for repeat consultations.[6] For some patients, the severity of dry eye disease and its chronicity lead to mood (affective) alterations and depression.[50] The potential impact of dry eye on an individual's perception of their health is substantial and of importance as a public health problem.[48] The possibility of a role for psychiatric and neurological disorders in patients with dry eye disease appears to be more likely for patients for whom signs and symptoms are discordant.[85] Consequently, that dry eye symptoms may be more or less unrelated to objective signs of ocular surface disease[7,8] allows for the possibility that those symptoms are appreciably determined by conditions such as neuropathy and/or mental health conditions. There are many forms of pain whose cause is unknown.[25] and, in the case of dry eye disease, may be due to a failure to consider neuropathy and mental health conditions as possible contributing factors in patients reporting dry eye symptoms.

The presence of anxiety and depression adversely effects treatment outcomes for comorbid conditions such as dry eye disease[86] and management which is limited to treatment for tear homeostasis anomalies would be less appropriate in such cases. Polypharmacy may be another contributing factor for dry eye symptoms and anti-depressant medications, diuretics, anti-histamines, psychotropics, cholesterol lowering agents, beta blockers, and oral contraceptives need to be considered during management.[87] However, that a definite association between depression and dry eye disease was found in patients with newly diagnosed (untreated) depressive disorders suggests that anti-depressive selective serotonin uptake inhibitors for example, are not necessary conditions for the development of dry eye symptoms in depressed patients.[88] Apart from treatment of lacrimal functional unit anomalies, counselling and medication for mental health conditions may be required in order that optimum outcomes are achieved for patients with dry eye disease. However, despite having the potential for a favourable response to treatment, depression for example, remains largely undetected and untreated.[57] A survey of a sample of 100 ophthalmologists and optometrists (with 30% identifying themselves as dry eye specialists) found that only 30% listed anxiety or depression among dry eye disease comorbidities[16] That finding suggests that comorbid mental health disorders may not be receiving enough consideration in the management of dry eye disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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