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 Review

MENTAL DISORDERS AS INFLUENCING FACTORS FOR DISCORDANCES IN THE SIGNS AND SYMPTOMS OF DRY EYE DISEASE

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SUMMARY

Dry eye disease (DED) is a multifactorial disease of the tear film and ocular surface representing one of the most common problems in ophthalmological practice. Characteristic symptoms of DED include gritty, sandy foreign body sensation as well as visual disturbances that have a negative impact on the patient's daily activities and social life. It is often assumed that the symptoms of dry eye are the main features of this disease, however, the symptoms do not always coincide with the signs and the results of diagnostic tests and the cause of this discordance in perception is still unclear. Numerous studies have been conducted in order to determine the cause of these discrepancies. Mental health disorders may be one of considerable contributing factors for dry eye symptoms and undiagnosed mental health conditions can be an influencing element for unexplained levels of DED symptoms. Depression, anxiety, stress, hypochondriasis, neuroticism, sleep and mood disorders may be associated with the exacerbation of symptoms to degrees that are not consistent with the objective signs related to tear dysfunction as well as changes in the anterior surface of the eye. Thus, a detailed medical history, thorough ophthalmological examination and referral to a psychologist or psychiatrist may be essential in the treatment of patients whose symptoms do not correlate with objective evidence of DED

Key words: *mental disorders - dry eye disease – symptoms – signs - quality of life - dry eye syndrome questionnaires*

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INTRODUCTION

Dry eye disease (DED) is a multifactorial, progressive and chronic disease of the tear film and ocular surface representing one of the most common problems in ophthalmological practice (Behrens at al. 2006, Kaštelan et al. 2013a,b). Characteristic symptoms of DED include dryness, discomfort, sandy foreign body sensation, tears, pain, burning, itchiness as well as visual disturbances. These symptoms have a significant negative impact on the patient's social life, daily activities and quality of life (QOL). Tears protect the ocular surface from infection in severe cases of untreated DED. The associated inflammation can damage the conjunctiva and the cornea with an increased risk of eye infection, which can cause irreparable ulceration or scarring (Jackson 2009, Kaštelan et al. 2013a).

Due to the diversity in the clinical presentation of DED, it is necessary to reach a consensus regarding the definition that would facilitate diagnosis and standardized treatment. Currently there is no widely accepted agreement and a possible reason could be the reported low correlation between the severity of symptoms and clinical diagnostic test results (Smith et al. 2007, Sullivan et al. 2014, Szakáts et al. 2016, Nichols et al. 2004, Johnson 2009). Over the years, various professional organizations have proposed different definitions and diagnostic criteria for DED. In recent decades, the pathophysiology of the disease is better understood, leading to changes and improvement of the definition and classification. The Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) in 2017 defined DED as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (Craig 2017, Tsubota et al. 2020).

PREVALENCE OF DRY EYE DISEASE

The prevalence of dry eye symptoms was observed in the range of 5% to 50%, with substantial variation between countries, depending on the study population and the definition used (Gayton 2009, Farrand 2017, Schaumberg et al. 2003, Kaštelan et al. 2013a, Smith et al. 2007, Stapleton et al. 2017, Kloosterboer et al. 2019). This large discrepancy in prevalence is presumed to be the result of a combination of factors such as geographical location, study population variations and

lack of consistent diagnostic criteria. The existing prevalence is expected to increase due to ageing population and stressful social circumstances. Further, the growing use of video display units is leading to an additional increase in prevalence particularly among the younger population (Donthineni et al. 2021).

DRY EYE DISEASE – AETIOLOGY AND RISK FACTORS

Adequate production, excretion and elimination as well stability of tear film are important for maintaining health of the eye surface. The tear film consists of three distinct layers: a thin outer lipids layer secreted by Meibomian glands, an inner mucin layer secreted by conjunctival goblet cells and middle aqueous layer secreted by the lacrimal and accessory glands. A newer concept describes the tear film as a dynamic mucinous gel that decreases in density from the inner to the outer layer with recent studies suggesting that there may not be a clear boundary between the mucin and aqueous phases, leading to a two-layer film model (Kloosterboer et al. 2019). The tear film is essential for maintenance of the structure and functioning of the cornea, namely the optically clear surface, nourishing and lubricating the eye tissue, washing away foreign bodies and cell debris and protecting from bacterial infections (Jackson 2009, Kaštelan et al. 2013a). Inflammation is an important feature of DED particularly in patients suffering from systemic autoimmune disease. Conjunctival inflammation is manifested by infiltration of inflammatory cells and up regulated expression of immune markers. Hyperosmolar stress, which accompanies the evaporation of tears, has an additional pro-inflammatory effect. A better understanding of the immunopathological mechanisms responsible for the development of ocular surface disorders corresponds to modification of applied therapy (Kaštelan et al. 2013a).

Risk factors for the occurrence of dry eye include older age, female sex gender and race or ethnicity with greater incidence in patients of Chinese, Hispanic, Asian, and Pacific Island descent. Women are more susceptible to dry eye symptoms, particularly those who are receiving estrogen replacement therapy. Additional risk factors include computer use, contact lens wear, a diet low in omega-3 essential fatty acids, refractive surgery, vitamin A deficiency, radiation therapy, bone marrow transplantation, connective tissue diseases, systemic cancer chemotherapy, hepatitis C, some systemic medications and environmental conditions of low humidity. (Smith et al. 2007, Moss et al. 2000, Kaštelan et al. 2013a,c, Pili et al. 2014). Likewise, several epidemiological studies reported higher prevalence of DED in patients with psychiatric disorders such as depression, anxiety, schizophrenia, bipolar disorders, neuroticism and stress implicating the influence of psychiatric and psychogenic factors on DED symptoms. (Galor et al 2015, Wen et al. 2012, Ichinohe et al. 2012, Liang et al. 2020, Szakáts et al. 2016, Kuang et al. 2020, Fernandez et al. 2013, Dibajnia et al. 2012). In addition, medications used in the treatment of depression including antidepressants with anticholinergic effect (Wong et al. 2011), selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors may additionally increase risk of dry eye (Mrugacz et al. 2017).

DIAGNOSIS OF DRY EYE DISEASE

DED is a multifactorial condition that is frequently encountered in ophthalmic practice. It has a different presentation with the symptoms and signs of the disease often having a weak correlation and therefore diagnosing DED can be very challenging. A systematic approach that takes into account the patient's symptoms including local and systemic medications, possible risk factors as well as careful clinical examination should be applied (Table 1). To obtain an accurate insight into the symptoms and objective signs of dry eye, diagnosis is based on the quantification of subjective symptoms through specialized questionnaires and thorough examination of the eye (Donthineni 2021, Manigione et al. 2001, Schiffman et al. 2000, Kaštelan et al. 2013a, Sullivan et al. 2014, Zheng et al. 2017, Klosterboer et al. 2019, Abetz et al. 2011, Sakane et al. 2013).

Table 1. Signs and symptoms of dry eye disease

Signs
Abnormal TBUT (less than 10 sec)
Abnormal Schirmer test (less than 5 mm)
Corneal and/or conjunctival staining: fluorescein, rose bengal, lissamine green
Abnormal tear meniscus height (less than 0.2 mm)
Abnormal tear osmolarity
Meibomian gland dysfunction
Limbal and/or bulbar hyperaemia
Lid margin vascularization
Lid margin laxity and/or irregularity
Symptoms
Dry eyes sensation
Sandy foreign-body sensation
Discomfort
Grittiness
Burning sensation
Tearing
Pain
Photophobia
Frequent or repeated blinking
Visual disturbances

TBUT: tear break-up time test

Table 2. Dry eye questionnaires with questions regarded QOL and psychometric properties: good validity and reliability according to the PRO guidance

Questionnaire, Year of development	Aim	Number of question	Points range	Cut-off value
OSDI, 1997	Visual function, QOL, severity of symptoms, environment triggers	12	0–100 for the total score and each subscale	Mild 13–22 Moderate 23–32 Severe 33–100
IDEEL, 2003	Symptoms, visual function, QOL, treatment satisfaction	57	0–100 for each module	None
DEQS, 2013	Symptoms, visual function, QOL	15	0–100	15
UNC DEMS, 2014	Symptoms, QOL	1 single item scale	0–10	None
CDERQOL, 2017	Symptoms, QOL, treatment satisfaction	45	5–225	None
NEI VFQ-25, 2001	Visual function, QOL	25	0–100 for each question	None

QOL: quality of life; PRO: patient reported outcome; OSDI: Ocular Surface Disease Index, IDEEL: Impact of Dry Eye in Everyday Life, DEQS: Dry Eye-Related Quality-of-life Score, UNC DEMS: University of North Carolina, Dry Eye Management Scale, CDERQOL: Chinese version of Dry Eye-Related Quality of Life, NEI VFQ-25: 25-Item National Eye Institute Visual Function Questionnaire

DRY EYE SYNDROME QUESTIONNAIRES

Over the past two decades, there has been an increasing emphasis on the history and symptoms in the diagnosis of DED. A verified symptom questionnaire may be used at the beginning of each examination to monitor the progress and effectiveness of treatment. A comprehensive questionnaire assessing the symptoms and impact of DED on QOL has shown to be as important as clinical findings themselves. The selection process of a dry eye questionnaire must take in to account several factors. It must be able to detect and measure changes in symptom intensity in response to treatment or disease progression as well as having an adequate description of psychometric properties with emphasis on patient-reported outcomes (PRO). Further it needs to be sensitive enough so as detect the therapeutic response of the drug and must be reproducible (Shiraishi & Sakane 2018, Okumura et al. 2020).

Currently, various questionnaires exist in clinical practice regarding subjective dry eye symptoms. Each questionnaire has specific advantages and reflects the impact of DED on daily health-related function and QOL (Craig et al. 2017). Evaluation of symptoms has shown to be important in diagnosing DED and therefore, questionnaires addressing the symptoms and impact of DED on QOL have gained in importance as an assessment tool. There is a recommendation for their use at the first examination since they allow rapid and efficient collection of relevant information and can facilitate the diagnosis of ocular surface disorders. Unfortunately, to date there is still no generally accepted standardized questionnaire available. However, there are several that include questions regarded QOL and which have good psychometric properties with validity and reliability according to the PRO guidance (Table 2) (Abetz et al. 2011, Sakane et al. 2013, Grubbs et al. 2014, Zheng et al. 2017, Mangione et al 2001, Okumura, et al. 2020).

OBJECTIVE TESTING

In addition to assessing subjective symptoms it is important to combine the questionnaire results with an ophthalmological examination including measurement of tear break-up time (TBUT), measurement of tear excretion using the Schirmer test, ocular surface staining with fluorescein sodium, lissamine green or rose bengal, as well as tear osmolarity (Kawashima et al. 2020, Kaštelan et al. 2013a, Okumura et al. 2020).

TBUT is the most commonly used test for the determination of tear film quality and stability. Fluorescein is applied into the lower fornix and a broad slit-lamp beam with cobalt blue filter is used to scan the tear film. The presence of black spots or lines is an indicator of tear film rupture and an interval between blinking and the appearance of the first randomly distributed dry spot in less than 10 seconds is considered abnormal (Jackson 2009, Kaštelan et al. 2013a).

Fluorescein is also useful in assessing dry eye where its application can determine the integrity of the corneal and conjunctival epithelium. The normal epithelium does not stain; however, in the case of a damaged mucin layer, the dye penetrates and stains the epithelium (Jackson 2009, Kloosterboer, et al. 2019). Lissamine green is another dye used to evaluate the anterior

segment and is used to stain dead or degenerated cells and produces less irritation compared with rose bengal dye (Kaštelan et al 2013a).

The most widely used technique to evaluate tear quantity is the Schirmer test I, performed without anaesthetic. In this test, a strip of filter paper is placed for 5 minutes under the lower eyelid on the temporal side. The length of the moistened strip is measured with results of less than 5 mm show aqueous tear deficiency (Jackson 2009, Kaštelan et al. 2013a). Another non-invasive method used is measurement of the tear meniscus height on the lower eyelid, where heights less than 0.2 mm are associated with tear deficiency (Kaštelan et al. 2013a, Kloosterboer et al. 2019).

Some authors consider that the determination of tear osmolarity is significant in dry eye diagnosis; however, it requires expert technical support, and its use has to date been confined to specialized laboratories. The availability of new more affordable osmometers will spread their use in everyday practice (Kloosterboer et al. 2019)

MENTAL STATUS AND DRY EYE SYMPTOMS

A number of epidemiological studies have investigated the association of depression and anxiety with DED reporting that subjective symptoms of dry eye may be affected by psychological factors such as depression, anxiety, post-traumatic stress disorder, bipolar disorders and subjective happiness (Szakats et al. 2016, Kawashima et al. 2015, Vehof et al. 2017, Galor et al. 2015, Hallak et al. 2015, Kitazawa et al 2017, Ayaki et al. 2015, Weatherby et al. 2019, McMonnies 2021). Several studies showed that dry eye patients were more anxious and depressed than healthy participants (Galor et al. 2015, Kawashima et al. 2015, Szakáts et al. 2016, Li et al. 2011, Kim et al. 2011, Liang et al. 2020). On the other hand, interferences associated with DED led to a further increase in anxiety. This implies that diagnosis of DED based only on symptoms may be incorrect, since the intensity of symptoms may be influenced by mental status of the patient (Szakáts et al. 2016).

We are often faced with the fact that subjective symptoms may not be explained by ocular findings. In the study performed by Szakats et al. (2016) 14.2% of patients presenting with typical dry eye symptoms, had no DED as measured by the objective parameters. Alternatively, 82.1% of the asymptomatic subjects showed objective evidence of dry eye. Significantly lower health anxiety, depression, and anxiety scores were observed in the asymptomatic group. These results support the idea that patients with objectively proven dry eye in the asymptomatic group may be less aware of dry eye symptoms, even in the presence of the disease. Since health anxiety and symptoms of depression and anxiety showed significant positive correlations with the intensity of dry eye symptoms, the authors proposed that they are responsible for heightened perception of symptoms even in cases where an organic cause can be excluded by the objective tests. In fact, after comparing asymptomatic and dry eye symptomatic patients, the scores for depression and anxiety according to psychological questionnaires were significantly worse in the symptomatic group. Kawashima et al. (2015) conducted a study regarding the association between subjective happiness and objective and subjective symptoms of DED in a group of young office workers using visual display terminals. They found that 21.6% of the participants showed objective evidence of DED without subjective dry eye symptoms. They proposed that study participants with high subjective happiness scores tend not to focus on their symptoms of eye dryness and thus may be less likely to report symptoms of dry eye even in the presence of objective signs of the disease. Vehof et al. (2017) described chronic pain syndrome, osteoarthritis, atopic diseases, depression and the use of antidepressants as predictors of symptoms being more pronounced than the physical signs of DED. Similarly, Galor et al. (2015) reported that for some patients, dry eye symptoms could align more closely to conditions such as non-ocular pain, depression and posttraumatic stress disorder rather than to tear film parameters. Depression is a major problem in general with a prevalence of 10-15% in the age group over 65 and more common in those with physical illnesses (Hallak et al. 2015). An association between depression and dry eye symptoms has been established and patients showing signs of clinical depression perceived dry eye symptoms as more severe (Hallak et al. 2015, Kitazawa et al 2017). Ayaki et al. (2015) reported that sleep and mood disorders was significantly associated with the prevalence of dry eye with the quality of sleep having a positive correlation with the severity of DED. Further, sleeping disorders are proven to be related to depression and anxiety disorders (Weatherby et al. 2019, McMonnies 2021).

Successful treatment of depression leads to improvements in dealing with comorbid diseases including DED. Equally, effective treatment of DED may have a positive impact on the mental status of patients. Ideally, for proper management, the treatment of dry eyes should be combined with therapy for depression and anxiety. Effective treatment of DED may help relieve symptoms of depression, and vice versa, appropriate management of depression could help alleviate symptoms of dry eye. However, some anti-depressive and anti-anxiety medications such as antidepressants with anticholinergic effect and selective serotonin reuptake inhibitors may exacerbate DED (Kitazawa et al. 2018, McMonnies 2021).

DISCORDANCES IN THE SIGNS AND SYMPTOMS OF DRY EYE DISEASE

Mental status may explain discrepancies in reporting intensity of DED symptoms. Anxiety, depression, hypochondriasis, stress, sleep and mood disorders as well as neuroticism, may be associated with an aggravation of symptoms to degrees that are not consistent with tear status observed during ophthalmological examination (Wen et al. 2012, Ayaki et al. 2015, Kuang et al. 2020, Li et al. 2011, Hallak et al. 2015, Szakats et al. 2016, Kitazawa et al. 2018, McMonnies 2021).

There is a possibility that the subjective symptoms are influenced by psychiatric or psychogenic factors. Some researchers have reported finding a significant relationship between a patient's symptoms and his psychogenic status suggesting that these links may need to be considered (Wen et al. 2012, Hallak et al. 2015, Labbe et al. 2013, Kim et al. 2011, Na et al. 2015, Fernandez et al. 2013). In addition, sensitivity to pain has been reported to play a significant role in the severity of DED complaints (Galor et al. 2015, Vehof et al. 2013), which also suggests the importance of non-ocular status of patients with DED symptoms.

Association between self-reported symptoms and clinical examination of DED are rarely described, posing difficulties in clinical treatment and research of dry eye (McMonnies 2021, Sullivan et al. 2014, Okumura et al. 2020, Shiraishi & Sakane 2018, Nichols et al. 2004, Mizuno et al. 2010). The diagnosis, evaluation of severity and therapeutic approach to DED are further complicated by the variability of signs and symptoms, the absence of consensus in diagnostic criteria and inconsistencies between subjective symptoms and clinical results (Smith et al. 2007, Sullivan et al. 2014, Nichols et al. 2004, Johnson 2009, Szakáts et al. 2016). Lu et al. (2018) reported a poor consistency of dry eye symptoms assessed based on questionnaire responses and clinical examination results. Schein et al. (1997) surveyed dry eye symptoms in 2,249 elderly people and found that the Schirmer I test value did not correlate with the frequency of symptoms. Nichols et al. (2004) found no connection between dryness and foreign body sensation of dry eye patients and tear meniscus height, the phenol red thread, the Schirmer I test value and corneal fluorescein staining. Sullivan et al. (2014) failed to find a consistent relationship between common signs and symptoms of DED. The presence of atopic diseases, allergies, the use of antihistamines, chronic pain syndrome, depression and the use of anti-depressants are recorded as possible predictors of symptoms being greater than the actual signs of DED. Further, predictors of symptoms being less pronounced than signs of DED include ageing, the presence of Sjogren's syndrome and graft-versus-host disease (Vehof et al. 2017).

Several mechanisms may explain the existence of discrepancies between subjective self-reporting and clinical findings.

Inflammation plays a role in the pathogenesis of depression as well as DED. In tears and conjunctiva of patients with DED an increase in the production of a number of inflammatory cytokines was found. Likewise, patients suffering from depression, have higher levels of the same inflammatory cytokines and neuropeptides in their blood stream (Liang et al. 2020 Murgacz et al. 2017). This implies that the two diseases may have common pathologic mechanisms since the inflammatory cytokines found can simultaneously lead to inflammation of the ocular surface and worsening of symptoms of depression (Mrugacz et al. 2017, Kuang et al 2020).

Another factor contributing to the development of dry eye in patients with mental disorders are antidepressants and anxiolytic medications. They have potential side effects on the tear film due to their anticholinergic effect leading to decreased tear secretion (Moss et al. 2000, Kocer et al. 2015, Wan et al. 2016). Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, a newer generation of anti-depressants irrespective of the relatively mild side effects, are also significantly associated with an increased risk for DED. In fact, the Schirmer test I values were significantly lower in patients using SSRI and SNRI as compared to the control group (Wong et al. 2011, Kocer et al. 2015).

Personality traits and psychological factors influence the reporting of subjective symptoms of DED and may be an additional explanation for the weak association between the signs and symptoms. Alternatively, the disease symptoms themselves may affect the patient's personality (Ichinohe et al. 2016). In addition, high pain sensitivity and low pain tolerance have been reported to be associated with DED symptoms (Vehof et al. 2013), which are more closely related to non-ocular pain than to tear film parameters (Galor et al. 2015).

Further, patients suffering from depression and anxiety when compared with healthy controls describe ocular sensations differently which can be explained by their mood and pain perception. Since somatization is a common feature of depression, this could have an impact on the perception of ocular discomfort (Galor et al. 2015, Kawashima et al. 2015, Kim et al. 2011). Several previous studies have reported that patients suffering from depression have a lower pain threshold often complaining of more intense dry eye symptoms compared to non-depressed patients. "Neuropathic pain" caused by neural dysfunction plays a role in unreasonable chronic pain in patients with DES and depression (Liang et al. 2020).

IMPLICATIONS FOR TREATMENT

An understanding of the pathophysiology of the association of mental status and DED is important as it has significant clinical implications regarding the approach adopted to dealing with patients with DED. Conditions other than loss of tear homeostasis may contribute to dry eye symptoms and treatment aimed only at the restitution of impaired tear film stability may be less effective (McMonnies 2020). Despite the widespread prevalence of dry eye symptoms, ocular surface disease remains quite difficult to manage since objective clinical signs often conflict with patient-reported symptoms (Szakáts et al. 2016, Galor et al. 2015, Nichols et al. 2004, Sullivan et al. 2014).

Ophthalmologists managing dry eye patients should be aware of potential mental comorbidities in addition to ocular conditions and take in to consideration underlying mental disorders. In fact, it is not unusual for patients despite adequate treatment of DED to experience severe symptoms without concomitant eye surface disorders. In those patients, subjective symptoms are disproportionate to objective signs usually associated with anxiety, depression, or other mental health issues and are more aligned with their mental health status rather than tear film dysfunction. Appropriate screening and referral to a psychologist or psychiatrist may be the key to managing patients whose symptoms do not correlate with objective evidence of DED and in such cases, a multidisciplinary management approach is recommended (Wan et al. 2016).

CONCLUSION

Dry eye disease is one of the most common ophthalmological conditions and has become a major health problem due to its growing prevalence and impact on healthcare resources and QOL. In clinical practice it is not uncommon to observe discrepancies between the ocular signs and symptoms of DED with the symptoms being more aligned to non-ocular conditions rather than to the tear film parameters (Schein et al. 1997, Nichols et al. 2004, Galor et al. 2015). The severity of subjective symptoms of dry eye are often related to psychological factors and ophthalmologists treating dry eye patients should be aware of their potential mental comorbidities in addition to ocular conditions. Identification and management of underlying psychological disorders can therefore be a supplement to local therapy and improve the patient's subjective symptoms of the ocular surface and potentially their QOL. A holistic, multidisciplinary and personalized approach based on the severity and extent of the individual's condition is necessary to achieve optimal treatment results.

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Contribution of individual authors:

Snježana Kaštelan: idea, concept and design of article, literature searches, writing manuscript, approval of final version.

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