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DOCTORAL THESIS

(Summary)

Correlation between signs and symptoms in the clinical diagnosis of dry eye syndrome

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INTRODUCTION

The Latin term “keratoconjunctivitis sicca” refers to dry eye syndrome and inflammation of the cornea and conjunctiva, being introduced by Henrik SC Sjogren, a Swedish ophthalmologist, in 1950 and then reintroduced by Andrew De Roetth as “dry eye syndrome”. Histologically, dry eye syndrome was defined as a reduction of the aqueous layer of the tear film. In 1995, the definition was changed to include general and ocular disorders that reduce the production of tears and/or increase the evaporation of tears. Dry eye syndrome was defined as a tear film disorder caused by tear deficiency or excessive evaporation of tears, which affects the interpalpebral surface and is accompanied by symptoms of discomfort. (1,2, 3, 4)

In 2007, the International Dry Eye Workshop (TFOS DEWS I) reformulated the original definition and classified the dry eye syndrome as “a multifactorial condition of the tear film and the ocular surface, with symptoms such as eye discomfort, visual acuity alteration and tear film instability, with potential damage to the ocular surface. It is accompanied by increased tear film osmolarity and subacute eye surface inflammation”. The purpose of this report was to formulate a definition and classification of dry eye syndrome based on the etiology, mechanism and stage of the disease. (3)

The 2017 TFOS DEWS II report redefined dry eye syndrome as a multifactorial ocular surface disorder characterized by loss of tear film homeostasis and accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, ocular surface inflammation and damage, as well as neurosensory abnormalities play an etiological role. The inclusion of the etiological factor in the definition comes to accentuate the multitude of causes that lead to the appearance and aggravation of dry eye syndrome. Each definition stimulated the researchers and brought us closer to understanding dry eye syndrome. (4)

The epidemiology of this syndrome continues to be different from study to study, despite the standardized definition. This is because studies use different diagnostic criteria and different diagnostic tests. The prevalence of dry eye syndrome based on signs and/or symptoms is variable, as positive signs and symptoms vary between studies. (3,4)

The challenge in dry eye syndrome is to outline a set of tests and usual diagnostic criteria that can fully define this condition.

Worldwide, the concerns about dry eye syndrome are numerous, and the initiative of the TFOS DEWS reports is very important, as this syndrome affects over 30 million people in the United States alone and at least 344 million worldwide. (4)

In my practice as a clinical ophthalmologist, dry eye syndrome is one of the most common disorders of the ocular surface. Most often it is associated with other ocular and general disorders and has a variable symptomatology. The sensitivity and specificity of the diagnostic tests in this condition are dependent on age group, criteria for inclusion within this category of disease and the degree of severity.

The diagnosis and management of dry eye syndrome is still a challenge for the ophthalmologist, with many unanswered questions: is there an objective correlation between symptoms and diagnostic tests? Do diagnostic tests provide enough information for a correct diagnosis? Is the dry eye a cause of vision loss? Is there a connection between the values of contrast sensitivity and the stage of dry eye syndrome? Can treatment with tear substitutes show an improvement in contrast sensitivity in these patients? Is dry eye syndrome a curable condition?

There is no universally accepted consensus or “gold standard” in the diagnosis of dry eye syndrome; most diagnostic tests are poorly standardized, which makes it difficult to compare studies between different authors. The fact that some of these tests have a pathophysiology that has not yet been completely elucidated, and the symptoms of dry eye syndrome may interfere with the symptoms of other eye disorders, can lead to diagnostic errors. When the eye sensitivity is low due to advanced disease and the tests used are far from being perfect, the correlations between them are also poor. (3,4) All these statements are a good motivation for choosing this research topic.

The study will select the combination of diagnostic tests with the best accuracy, minimal-invasive, objective and clinically applicable. The symptomatology will be standardized using the OSDI questionnaire. Contrast sensitivity testing will be done in order to formulate a correct and complete diagnosis providing valuable information for the diagnosis and treatment of this condition.

GENERAL PART

The general part of the paper consists of chapters 1-4 and presents theoretic aspects related to the definition of dry eye syndrome, pathophysiology, anatomy, epidemiology, current diagnostic methods but also the differential diagnosis of this condition. The general part of the paper aimed at a review of the literature, which sought to browse and analyse the literature published in the field of the diagnosis of dry eye syndrome and to create the framework of a perspective, but also to identify studies that would support the chosen topic.

PERSONAL CONTRIBUTIONS PART

The personal contributions part of the work consists of chapters 1-7. The study group consists of 104 subjects, which were grouped and introduced into different study groups during the research, depending on the objectives aimed at. The control group consists of 11 subjects. The study group include patients with dry eye syndrome, 100 of them with evaporative dry eye syndrome and 4 of them with dry eye syndrome due to aqueous deficiency (associated with Sjögren's syndrome). The criteria for inclusion in the study and the methodology will be detailed in each chapter. The examination of patients was performed by the same investigator.

Chapter 1 of the personal part is entitled " The objectives of the research theme":

- one of the aims of our research is to correctly and completely evaluate the symptoms of dry eye syndrome, which is often undiagnosed and uncorrelated with clinical trials. The severity of symptoms can make a sub-classification of this condition.

- following this study we intend to find out the role of the OSDI questionnaire in the evaluation of symptomatology and to find out the advantages and disadvantages of the application of this questionnaire on mobile phone.

- highlighting the role of signs and symptoms with regard to classifying the dry eye syndrome in degrees of severity.

- based on the OSDI questionnaire in the extended version, we aim to find out which symptoms are the most commonly experienced by the patients in the study group, which are

the environmental factors that most influence the symptomatology, but also how the symptomatology has an effect on the daily activities.

- identification of the relationship between ocular symptoms and diagnostic clinical tests in dry eye syndrome.
- finding an optimal combination of diagnostic tests that are minimally-invasive, but at the same time providing the necessary information for a complete and accurate diagnosis.
- comparison of the results of our study with those of recent specialty literature.
- interpretation of the role of contrast sensitivity measurement in patients with dry eye syndrome.
- determination of the role of tear break up time in the diagnosis and evaluation of dry eye syndrome.

Chapter 2 is entitled "Symptomatology: the first step in the diagnosis of dry eye syndrome". The purpose of this study was to highlight the frequency of ocular symptoms, but also their effect on daily activities in those 75 patients with evaporative dry eye syndrome, using the OSDI questionnaire filled out in the classic version. After filling out the OSDI questionnaire, the patients underwent a complete ophthalmological evaluation. Diagnostic tests for dry eye syndrome were performed by the same examiner in the following order: Schirmer I test, tear break up time with fluorescein, corneal and conjunctival staining with fluorescein and lissamine green. The criteria for inclusion in the study were: patients with positive dry eye tests (Schirmer I <or equal to 10 mm test, tear break up time <or equal to 5 seconds and OSDI score> or equal to 11 points), with or without other general or ocular diseases, aged between 18 and 85. The mean age of the study group was 60 years (M = 61.87, SD = 11.70), the mean score of the OSDI questionnaire being M = 60.17, SD = 12.901. The most common symptom encountered in patients was the foreign body sensation while the air conditioning contributed most to the aggravation of the symptoms of dry eye syndrome.

Chapter 3, "Correlation between diagnostic tests and symptoms in dry eye syndrome", aimed at performing tests for dry eye syndrome but also at measuring contrast sensitivity in those 32 patients in the study group. Negative correlations were observed between OSDI score and tear break up time, Schirmer I test and contrast sensitivity, and positive correlations were observed between OSDI and Oxford scheme. Of these correlations,

only those between OSDI and tear break up time and contrast sensitivity were statistically significant.

Chapter 4 "Cluster analysis of the relationship between signs and symptoms in dry eye syndrome". The aim of this study was to analyse the relationship between diagnostic tests (Schirmer test, tear film breakup time tests, ocular surface staining) and symptoms of dry eye (ocular surface disease index questionnaire - OSDI) using a cluster analysis approach. The research was performed among 47 patients (32 with dry eye disease and 15 control subjects). For all performed tests the differences between dry-eye group and control group were statistically significant (OSDI score 47.03±19.86 vs. 8.53±3.72, tear break-up time 3.86±1.43 vs. 17.83±1.87, Schirmer test I 4.47±3.25 vs. 20.37±2.79, Oxford scheme 0.88±0.87 vs. 0±0.86). The cluster analysis procedure, in the context of our patient's data, estimate the following hierarchical discriminative importance of the tests results: tear break-up time (100%), Schirmer I Test(67%), OSDI (29%), Oxford scheme (12%). Tear film instability is a common link for all types of dry eyes and its evaluation can be crucial when there is no ocular staining and the tear volume is normal or abundant.

Chapter 5 "The role of contrast sensitivity in patients with dry eye syndrome". The purpose of this prospective observational study was to evaluate contrast sensitivity in dry eye patients using LCD CHART PROJECTOR (CC-100 Series 2015). Contrast sensitivity was determined in 42 eyes of 21 patients with dry eye (the dry eye group) and 22 eyes of 11 healthy volunteers (the control group) with normal (VA=20/20) corrected or uncorrected visual acuity. We measured the contrast sensitivity at 4 contrast levels using 9 grading frequencies. Analyses with the Mann-Whitney U test showed significant differences (CS lowering) between the study and control group from the spatial frequency of 4.24 cpd ($P=0.042<0.05$) to spatial frequency of 24 cpd ($P=0.000<0.05$).

Chapter 6 "General discussions and final conclusions"

The evaluation of the symptomatology plays an important part both in the screening, the diagnosis and in the monitoring of the efficiency of the treatment of the dry eye syndrome.

The OSDI questionnaire, both in the classic version and in the form of a mobile phone application, is very useful in evaluating the symptomatology of patients with dry eye syndrome. The classic version of the questionnaire, where the patient fills out and the

examiner calculates the final score, has the advantage that the patient's answers are detailed and the collected data can be analysed statistically. The variant of the questionnaire – phone application, where the examiner addresses the questions and tick the answers provided by the patient, the application automatically generating the OSDI score, is a quick way to evaluate the symptomatology. The disadvantage may be that we have only a final score, not the detailed answers, the statistical analysis of the detailed answers being impossible. The OSDI application generates a quick score, while the classic version by calculating the score may cause calculation errors.

The battery of diagnostic tests, used in clinical practice for the diagnosis of dry eye syndrome, must be composed of non-invasive but at the same time inexpensive tests, clinically applicable and capable of guiding the clinician towards a correct and complete diagnosis.

In this studies , tests were chosen that covered all the clinical aspects of dry eye syndrome: the OSDI questionnaire was used for the evaluation of the symptoms, the contrast sensitivity revealed subtle changes in the quality of vision in these patients, the tear break up time highlighted the stability of the tear film, the Schirmer I test measured the amount of tears and with the help of the special colourings and the Oxford scheme we highlighted ocular surface changes of different degrees.

The results obtained in our studies were compared with the data from the specialized literature. As a result of this comparison, we were able to observe both differences and similarities. A complete comparison is not possible because each study is designed differently, starting from the criteria for inclusion in the study, the diagnostic tests used and the biologic reference intervals considered.

Chapter 7 "Perspectives opened by the research topic"

This study guides us to approach the diagnosis of dry eye syndrome in a much more complex manner. The subjective aspect related to the symptomatology of patients with dry eye syndrome is of particular importance, but also the objective aspects, represented by the clinical tests, are those that guide the clinician towards an appropriate treatment.

The novelty of this study also consists of the use of contrast sensitivity in the routine diagnosis of dry eye syndrome. Measurement of contrast sensitivity has been found to be

particularly useful in patients who complain about fluctuations of vision that cannot be assessed by conventional visual acuity measurement methods.

Following the studies performed on different groups of patients and on the same groups, it can be concluded that the clinical tests that correlate with the symptoms are the elective tests in dry eye syndrome. Of all the clinical tests performed, tear break up time and contrast sensitivity were negatively and statistically significantly correlated with the OSDI questionnaire. In addition to the complete ophthalmologic examination, in patients with dry eye syndrome it is recommended to perform symptomatology assessment through the OSDI questionnaire, to measure tear break up time and contrast sensitivity.

The use of a homogeneous set of diagnostic tests may be useful because only such a complete comparison between clinical trials may be possible.

Keywords: dry eye syndrome, tear break-up time, contrast sensitivity, symptoms, correlation

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