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DRY EYE MANIFESTATIONS IN SJÖGREN'S SYNDROME

PH.D. THESIS ABSTRACT

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SIBIU

2013

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KEYWORDS

Dry eye syndrome, Sjögren's syndrome, OSDI questionnaire, tear film breakup time, Schirmer test, corneal staining, correlations, screening methods.

THESIS ABSTRACT

INTRODUCTION

Dry Eye Syndrome is a common cause of eye discomfort affecting a significant percentage of the population over 40 years. It is a multi-factorial disease resulting in tear film dysfunction, due to tear's insufficient quantity and / or quality, or increased tear film evaporation, potentially damaging the ocular surface. Prevalence of dry eye increases with age, studies show that it ranges from 5% to 30% in the adult population. Age and female gender are the most important risk factors for dry eye syndrome.

Dry eye syndrome is classified into two categories: aqueous deficient dry eye and evaporative dry eye. The first category implies that dry eye is due to a failure of lacrimal tear secretion and has two subgroups: Sjögren syndrome dry eye and non-Sjögren syndrome dry eye Evaporative dry eye is due to an excessive tear loss from the ocular surface in the presence of a normal tear secretion. It is important to note that the two categories are not mutually exclusive and that the disease originally belonging to one of the categories can coexist with and/or can cause dry eye by the other mechanism.

Diagnosis of dry eye syndrome is essentially clinical. It is based on the presence of typical symptoms - mostly common with other ophthalmic diseases, clinical examination and some specific tests, which evaluate the severity of the disease, guide the follow-up, and can help with the therapeutic decisions.

Thanks to a better understanding of the pathophysiology of dry eye, treatment of this disease has developed from the simple administration of artificial tears that improve hydration and lubrication of ocular surface, into true therapeutic strategies aimed at increasing natural production of tears constituents, preserving the integrity of the ocular surface epithelium, and

inhibition of inflammatory mediators. New therapeutic approaches have allowed a significant improvement in quality of life for many patients with dry eye syndrome.

Sjögren's syndrome is an autoimmune disease characterized by lymphocytic infiltration of salivary and lacrimal glands that causes oral and ocular dryness and production of autoantibodies. Sjögren's syndrome can be primary or secondary associated to other systemic diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory myopathies, scleroderma). Sjögren's syndrome is considered the second most common autoimmune disease after rheumatoid arthritis. Its prevalence ranges between 0.1% and 0.4% of the adult population. Women are particularly affected, with a ratio of 9:1 to men, with a peak in incidence around the age of 50.

Sjögren's syndrome diagnostic criteria require, in addition to the presence of ocular and oral symptoms and signs, the presence of objective immunological abnormalities: a nodular inflammatory infiltrate in accessory salivary gland biopsy (Chisholm focus score ≥ 3), or the presence of anti-Ro/SSA antibodies or anti-La/SSB antibodies. Secondary Sjögren's syndrome diagnosis requires the diagnostic criteria for primary SS associated with manifestations of other connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, etc.).

MOTIVATION

Dry eye, because of the discomfort it causes, is one of the main reasons for presentation to an ophthalmologist, especially among the elderly. In addition, in Sjögren's syndrome patients, the dryness is permanent, extremely unpleasant, involving ocular, oral, skin and other mucosal dryness, joint and musculoskeletal pains, chronic fatigue. All these are responsible for a significant deterioration of the patient's quality of life.

I therefore sought to assess signs and symptoms of dry eye in patients with Sjögren's syndrome for a diagnosis as quick and accurate as possible to establish a tailored treatment and hence an improvement in symptoms. Identifying patients with Sjögren's syndrome among those who have moderate to severe forms of dry eye is very important, because these patients need systemic treatment in addition to local measures aimed to improve ocular dryness.

PURPOSE OF THE STUDY

Throughout this study I analyzed the symptomatology and the objective clinical signs of dry eye in patients with Sjögren's syndrome and the possible correlations between them. The main correlations analyzed were between the results obtained at OSDI questionnaire, used as an indicator of severity of symptoms, and Schirmer test values, TBUT and corneal staining, used to quantify the severity of dry eye syndrome.

I also wanted to evaluate the sensitivity and specificity of OSDI questionnaire in the diagnosis of severe dry eye and whether it can be used as a screening tool to differentiate moderate from severe forms of dry eye.

MATERIALS AND METHODS

This paper is based on a prospective, observational study conducted in Sibiu County Hospital, Department of Ophthalmology and Centre d'Ophtalmologie Nantes, France from January 2010 to October 2012.

Of all patients presenting in both ophthalmology departments during that period with suggestive signs and symptoms of dry eye disease I have selected a total of 61 patients aged over 18 years diagnosed with primary or secondary Sjögren's syndrome in the rheumatology and internal medicine departments. The selected patients had moderate and severe forms of dry eye and they did not receive topical ophthalmic treatment in the last month. For the diagnosis of moderate and severe forms of dry eye I used the dry eye severity grading published by Benjamin D. Sullivan et al. in 2010. (Schirmer test values < 7 mm/5min, TBUT < 7 sec, OSDI score > 15) (Sullivan BD, Whitmer D, Nichols KK, Lemp MA et al. An Objective Approach to Dry Eye Disease Severity. Inv. Ophthalmol. Vis. Sci. 2010; 51(12): 6125-6130)

All selected patients were informed about the inclusion in the study and the noninvasive nature of the methods used. They consented to participate according to the Declaration of Helsinki on medical research involving human subjects. (WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects)

Patients filled out the OSDI questionnaire and underwent a complete eye examination including both corrected and uncorrected visual acuity, anterior pole and lids examination at the slit lamp, posterior pole biomicroscopy, evaluation of TBUT, Schirmer test and corneal fluorescein staining.

STATISTICAL ANALYSIS

I analyzed the data of 121 eyes from 61 patients diagnosed with Sjögren's syndrome (one monophtalmic patient) and moderate and severe forms of dry eye. Of these 30 patients had primary Sjögren's syndrome and 31 patients had secondary Sjögren's syndrome. 44 patients had moderate and 17 severe forms of dry eye. Considering the significant deviation from normality of the distributions of the studied variables, I used the nonparametric Mann Whitney U test for the statistical analysis of the data. (p values < 0.05 were considered statistically significant). To analyze the association between different pairs of variables I used nonparametric Spearman correlation (p value <0.05 indicates a statistically significant association). Receiver Operating Characteristics (ROC) curves were plotted to obtain the sensitivity and specificity of the variables studied in relation to moderate/severe form of dry eye.

RESULTS

Patients were aged between 33 and 86 years. The average age was 62.23 ± 11.23 years. Distribution by age decades of the patients shows a significant frequency in the 6th decade of life (34.42% or 21 patients), followed by patients over 70 years (27.86% or 17 patients). Only three patients were aged below 40 years. Of the 61 patients studied 52 were women (85%) and 9 men (15%).

In this study group 30 patients were diagnosed with primary Sjögren's syndrome (49.18%) and 31 patients with secondary Sjögren's syndrome (50.82%). In the secondary Sjögren's syndrome group most of the patients had associated rheumatoid arthritis (24 patients, 77.41%). Five patients were diagnosed with systemic lupus erythematosus (16.12%) and only two patients with scleroderma (6.45%).

For A OSDI score, which assesses the specific symptomatology of dry eye, the values ranged between 5 and 17. This shows the great variability of symptoms in patients with dry eye. For B OSDI score I found values between 2 and 9, showing also that there are large differences regarding patient’s assessment of discomfort caused by dry eye in routine activities such as reading, watching television, using a computer or driving the car. Section C of the questionnaire OSDI attempts to evaluate environmental factors as predisposing factors for ocular dryness (exposure to wind, dry atmosphere, air conditioning). The C OSDI score results ranged from 2 to 7. OSDI total score ranged between 30 and 69 with a mean of 48.36 ± 10.58.

Schirmer test values were rated between 0 and 7 mm/5min for the right eyes and from 0 to 6 mm/5min for the left eyes, with an average of 2.62 equal for both eyes. In the study group only 5 right eyes and 2 left eyes had Schirmer test values exceeding 5 mm in 5 min (8.19% and 3.33%, respectively). I also found a significant number of eyes (12 right eyes and 12 left eyes) that had values of 0 mm/5min. This is a feature of aqueous deficient dry eye found in Sjögren's syndrome.

Tear film breakup time values have ranged between 1 and 7 seconds for both eyes, with a mean of 3.21±1.38 sec. for the right eye and 3.08 ± 1.29 sec for the left eye. In most cases TBUT values were rated between 2 and 4 seconds (77.04% from the right eyes and 78.33% from the left eyes).

Regarding the corneal fluorescein staining values, they were between 0 and 4 for both eyes, with a median of 1 and the quartile deviation of 2, for the right eye and a median of 1 and a quartile deviation of 1 for the left eye. I obtained values for the corneal staining higher than or equal to 1 in 75.40% of cases for the right eye and in 86.6% of cases for the left eye. Only in 15 right eyes and 8 left eyes I have not noticed any point of corneal staining.

The data obtained from measurements made on the 121 eyes were statistically analyzed and the existence of an association between the results recorded in OSDI questionnaire (A, B, C, D and total OSDI scores) and objective clinical tests (Schirmer test, TBUT, corneal fluorescein staining) was assessed. Patients were divided into two groups according to the classification published by Sullivan: those with moderate and those with severe forms of dry eye. Patients with measured values of Schirmer test less than 2 mm/5min and TBUT values less than 3 seconds were classified as severe cases. 44 patients (72.13%) were classified as moderate and 17 (27.86%) as severe cases of dry eye. In the moderate group were 18 cases of primary Sjögren's syndrome (40.9%) and 26 cases of secondary Sjögren's syndrome (59.1%), of which 22 cases of rheumatoid arthritis.

In the moderate dry eye group were found statistically significant associations between A OSDI score, total OSDI score and Schirmer test values (r_s = -0.558, p = 0.0001 for A OSDI score, and r_s = -0.640, p = 0, 0001 for total OSDI score), or TBUT (r_s = -0.530, p = 0.0001, r_s = -0.636, p = 0.0001, respectively). Highly significant correlations were found between corneal staining values and the two scores (r_s = -0.583, p = 0.0001, r_s = -0.662, p = 0.0001, respectively).

For C OSDI scores I found a modest negative correlation with Schirmer test values (r_s = -0.274, p = 0.071) and TBUT (r_s = -0.320, p = 0.034). Instead, between C OSDI score and corneal staining the association was highly statistically significant (r_s = 0.456, p = 0.002).

Correlations between corneal fluorescein staining and both Schirmer test and TBUT values were statistically significant (p = 0.001).

In the group of patients with severe dry eye, significant associations were found between clinical test results and A OSDI score or total OSDI score. I found significant negative correlations for Schirmer test values (r_s = -0.574, p = 0.016 for A OSDI score and r_s = -0.627, p = 0.007 for OSDI score) and TBUT values (r_s = -0.525, p = 0.030 for A OSDI score and r_s = -0.501, p = 0.04 for total OSDI score). For corneal fluorescein staining values, the associations were significant with A OSDI score (r_s = 0.532, p = 0.028) and highly significant with total OSDI score (r_s = 0.736, p = 0.001).

Regarding C OSDI score I found significant associations with Schirmer test values (r_s = -0.599, p = 0.011) and the corneal staining (r_s = 0.496, p = 0.043), but not with TBUT values (r_s = -0.388, p = 0.124), In the moderate dry eye group I found significant correlations of C OSDI score with corneal staining and TBUT values, but not with Schirmer test values.

I also found a significant association between Schirmer test values and the degree of corneal staining (r_s = -0.498, p = 0.042).

Using the nonparametric Mann-Whitney U test I compared the values obtained in the two subgroups of patients, the moderate dry eye group (44 patients) and the severe dry eye group (17 patients), to see if there are statistically significant differences for the studied variables. The same analysis was applied to highlight the differences between the other two subgroups of patients: with primary Sjögren's syndrome (30 patients) and with secondary Sjögren's syndrome (31 patients).

Regarding comparative analysis of the results achieved in OSDI questionnaire, depending on the severity of dry eye syndrome, statistically highly significant differences (p = 0.0001) were obtained for A, B and C OSDI scores and for the total OSDI score. The same significant difference was found for the three clinical tests: Schirmer test, TBUT and corneal staining. The biggest differences between groups were recorded for Schirmer test values (median 3.5 for the

moderate group and 0 for the severe one). Tear secretion decreases as the disease is more advanced.

ROC curve (Receiver Operating Characteristic) were plotted to obtain specificity and sensitivity for the studied variables in relation to moderate/severe dry eye. I sought to identify variables with potential of prognostic index for severe dry eye. Variables above the reference line can be used as screening tools to differentiate the moderate from the severe form of dry eye. Values higher than 0.5 for the area under the curve (AUC) for all OSDI scores (AUC between 0.804 and 0.955) were obtained. The sensitivity of OSDI total score in differentiating moderate form from severe form of dry eye was 88.2% and specificity 83.7%, at a threshold of 52 for the total OSDI score. Values of A OSDI score greater than 12.5 indicate, with a probability of error less than 1%, the presence of severe dry eye.

I further analyzed the results according to the type of Sjögren's syndrome. The average age of patients in primary Sjögren's syndrome group was 65.63 ± 12.03 years compared to the group of patients with secondary Sjögren's syndrome where the average age was 58.53 ± 9.36 years. The difference is statistically significant ($p = 0.019$).

Statistically significant differences between the groups of patients with primary and secondary Sjögren's syndrome were found for A OSDI score ($p = 0.005$), D OSDI score and total OSDI score ($p = 0.017$ and $p = 0.014$, respectively) and also for Schirmer test values ($p = 0.036$).

DISCUSSIONS

Sjögren's syndrome remains an underdiagnosed disease because of symptoms diversity and lack of specificity. Development of specific tests to assess symptoms and clinical signs would allow an early diagnosis and establishment of appropriate treatment, which would considerably improve the patient’s quality of life and may decrease the risk of serious complications (whose incidence remains high in the primary Sjögren's syndrome).

The results of this study showed that the simultaneous presence of positive clinical tests and characteristic symptom of dry eye is more suggestive for the diagnosis of Sjögren's syndrome as the symptoms are more severe. Diversity of symptoms at onset delayed diagnosis. It is estimated that on average 6 to 7 years pass between appearance of the first symptoms and the diagnosis. Early diagnosis and establishment of appropriate treatment would improve the

patient's quality of life and may decrease the risk of serious complications. Therefore, in the presence of characteristic symptoms interdisciplinary collaboration and physician's awareness are required for rapid diagnosis.

On the other hand, the characteristic symptoms of dry eye (burning sensation, sore eyes, gritty eyes, blurred vision) is one of the main reasons for presentation to the ophthalmologist. This brings into question the role of the ophthalmologist in Sjögren's syndrome screening and patient's orientation to rheumatology services in order to initiate the systemic treatment. Ophthalmologists should be more aware of Sjögren's syndrome whenever ocular dryness is accompanied by dry mouth, arthralgia or chronic fatigue.

Studies show that the incidence of Sjögren's syndrome in patients with dry eye syndrome is not negligible and systematic testing for SSA and SSB antibodies in severe forms of dry eye allows identifying a large number of cases of Sjögren's syndrome. In this study I have shown that in severe cases of dry eye (Schirmer test values less than 2 mm/5min., TBUT less than 3 sec.) for which OSDI score is higher than 45, Sjögren's syndrome must always be suspected. In these cases dosage of SSA and SSB antibodies is required, and if the results are negative, biopsy of oral mucosa.

Unfortunately there is no specific immunological marker of disease. SSA antibodies occur in 70-75% and SSB antibodies in 50-60% of Sjögren's syndrome cases. They must be interpreted in the clinical context and negative result of autoantibodies does not exclude the disease. Therefore, if symptoms and other clinical tests are evocative for Sjögren's syndrome, the oral mucosa biopsy must be performed to evaluate the lymphocytic infiltration of salivary accessory glands.

For the diagnosis of dry eye careful history is as important as clinical examination. The 2007 DEWS report established diagnostic criteria and the degrees of dry eye severity (The definition and classification of dry eye disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop (2007). 2007, 5 (2): 75-92). However there are no uniform diagnostic criteria. Classically, a combination of symptom assessment, using questionnaires, and specific clinical tests is used in dry eye diagnosis. This combination is necessary in patients with significant clinical signs but less expressed symptoms, and vice versa.

Regarding clinical tests used in the diagnosis of dry eye, Schirmer test remains an important indicator of aqueous tear deficiency. Even if the test is part of Sjögren's syndrome

diagnostic criteria, its importance is not universally accepted. Even if in mild and moderate cases of dry eye Schirmer test doesn't have an important diagnostic value, a test value less than 5 mm/min is considered a good indicator of aqueous tear deficiency. This study shows that there is a significant association of Schirmer test (for values less than 7 mm/5min) with OSDI scores for both forms, moderate and severe dry eye ($p = 0.0001$ and $p = 0.007$). Patients with primary Sjögren's syndrome have a more pronounced symptomatology and Schirmer test values lower than in patients with secondary Sjögren's syndrome. In this study the difference was statistically significant ($p = 0.036$).

Symptoms assessment plays a very important role in dry eye diagnosis. The study of symptoms made in recent years a significant contribution towards understanding the disease, possibly due to substantial improvements in measurement techniques. OSDI questionnaire was designed for rapid assessment of symptoms of dry eye.

In this study, OSDI questionnaire was a reliable instrument in the diagnosis of dry eye syndrome, especially in Sjögren's syndrome moderate and severe forms of dry eye. The ROC analysis has shown that all OSDI scores can be used as screening tools for severe dry eye (AUC > 0.808).A OSDI score and OSDI total score (AUC = 0.941, 0.955 respectively) had a higher sensitivity in detecting severe forms. Significant correlations between A OSDI score and total OSDI score were found for all assessments.

Similar results that we found for the two scores (A OSDI and total OSDI) could justify to use in practice, in a first stage, only the A OSDI score. If its value is higher than 12.5, the presence of severe dry eye is indicated with a probability of error less than 1% and is no longer necessary to continue the questionnaire. Further studies are needed to confirm if it's possible to use only A OSDI score for the screening of moderate and mild forms of dry eye.

OSDI questionnaire allows quick orientation toward dry eye syndrome, but fails to differentiate between evaporative and aqueous deficient form. Assessment of symptoms is even more important as there is no clinical test accepted as gold-standard in the dry eye diagnosis.

Initial diagnosis involves determining the presence of dry eye and only then the subtypes: evaporative or aqueous deficient. In my opinion, evaluation of the conjunctival hyperemia, blink frequency or diurnal variations of dry eye symptoms are also important in diagnostic orientation toward a particular subtype of dry eye. For a more comprehensive analysis of symptoms I suggest adding some questions to the OSDI questionnaire, allowing an analysis of

diurnal variation of symptoms. This would allow orientation toward aqueous deficient or evaporative form of dry eye, permit to choose better clinical diagnostic tests and better therapeutic decisions.

Further studies might show whether only the A OSDI score could be used for screening of various forms of dry eye or a questionnaire with more questions would be more appropriate for fast screening and orientation towards a specific form of dry eye. Further research on larger groups of patients might confirm the results of this study and bring new information regarding diagnostic and therapeutic orientation in dry eye syndrome.

CONCLUSIONS

Sjögren's syndrome has a higher incidence among women. In the study group 85% were women and the mean age was 62.23 ± 11.23 years. Most patients were in the age groups 51-60 years and over 70 years.

OSDI questionnaire proved in this study to be a reliable instrument in the diagnosis of dry eye syndrome, especially in moderate and severe forms of ocular dryness found in Sjögren's syndrome. At a threshold of 45, the sensitivity of the total OSDI score to differentiate between moderate and severe dry eye was 94.1% and specificity of 62.8%, while at a threshold of 52, specificity increased to 83, 7%, at a sensitivity of 88.2%. OSDI questionnaire can be used as a screening tool for severe dry eye.

OSDI score values higher than 12.5 indicates, with a probability of error less than 1%, the presence of severe dry eye. Severe forms of ocular dryness are characteristic to Sjögren's syndrome and therefore any A OSDI score value higher than 12.5, in a suggestive clinical context, should raise the suspicion of autoimmune etiology of dry eye syndrome.

Statistically significant differences were found between moderate and severe forms of dry eye for all studied variables (OSDI scores, Schirmer test values, TBUT, and corneal fluorescein staining).

For Sjögren's syndrome moderate forms of dry eye were found statistically significant correlations between A OSDI score, OSDI total score and clinical tests (Schirmer test values, TBUT, corneal staining). Results were similar in the case of Sjögren's syndrome severe dry eye. This shows that in Sjögren's syndrome associations between clinical signs and symptoms remain significant regardless of the severity of dry eye syndrome.

In patients with Sjögren's syndrome, statistically significant association were obtained between corneal staining values and Schirmer test values for both degrees of severity of dry eye syndrome (moderate and severe). In these patients the correlation between corneal staining, and TBUT values were significant for the moderate form, but not for severe disease. TBUT values do not correlate with OSDI score when there is no objective evidence of impairment of the corneal surface (negative corneal staining).

Schirmer test remains an important criterion in the diagnosis of aqueous deficient dry eye. In this study group the mean Schirmer test value was 2.62 mm/5minute.

Regarding comparative analysis between the groups of patients with primary and secondary Sjögren's syndrome, statistically significant differences were found for A OSDI score, total OSDI score and Schirmer test values. The symptomatology and lacrimal secretory deficiency were more expressed in primary Sjögren's syndrome group.