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Prevalence of dry eye in systemic lupus erythematosus patients of a tertiary referral center

Abstract

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multipleorgans, primarily young women. Ophthalmic complications, particularly dry eye, are common, occurring in approximately 16% of patients. This study aims to estimate the prevalence of dry eye in SLE patients from a tertiary referral center and assess its correlation with clinical and laboratory parameters.

Methods: This cross-sectional study was conducted between September 2021 and September 2022at the Professor Edgar Santos University Hospital (HUPES) and Medical Ophthalmology Services (SEMOF). Patients underwent various ophthalmologic tests, including theSchirmer test, break-up time test (TBUT), fluorescein, and lissamine staining, evaluatedby a single ophthalmologist. Dry eye symptoms were assessed using the Ocular Surface Disease Index (OSDI) questionnaire.

Results: The study included 114 patients (228 eyes), with a median SLEDAI of 4.01. Schirmer I test results ranged from 0 to 35 mm in both eyes, TBUT had a mean value of 6.7±2.2 seconds, and Lissamine Green staining had a mean value of 1.7±1.9. Median OSDI was 16.66. Applying the dry eye diagnosis criteria, 46.5% of patients met the requirements. An association was found between dry eye and anti-SSB antibodies and older age but not with disease activity.

Conclusion: Dry eye is a significant ocular complication in SLE, impacting patients' quality of life. Standardized diagnosis is crucial for harmonizing research findings across different cohorts and enabling targeted therapeutic approaches.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease of the connectivetissue that affects multiple organs. It mainly affects young women, and most studies showthat about one-third of these patients have some ophthalmic alteration, with dry eye beingthe main one, affecting approximately 16% of individuals.[1]

The clinical presentation can vary from superficial punctate keratitis in mild cases to filamentary keratitis and corneal ulcers in severe cases (Figure 1 & 2). The treatment depends on the severity of the condition and may include lubricating eye drops, topical corticosteroids, cyclosporine eye drops, and lacrimal punctal occlusion.

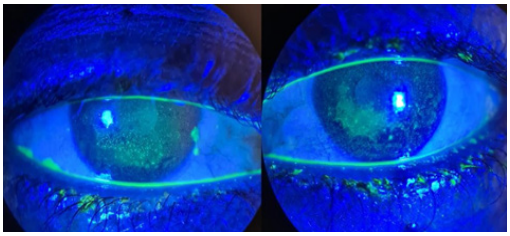

Figure 1 Diffuse superficial punctate keratitis in a lupus patient with dry eye.

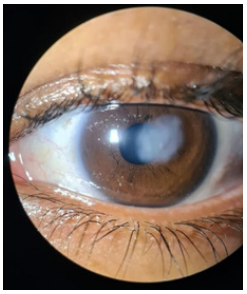

Figure 2 Corneal leucoma secondary to cornealulcer due

The objective of this study is to estimate the prevalence of dry eye in a sample of patientsfrom a tertiary referral center and correlate it with clinical data and laboratory parameters to severe dry eye in a lúpus patient.

Methods

This cross sectional study was conducted at the Rheumatology and Ophthalmology Services of the Professor Edgar Santos University Hospital (HUPES) and the Medical Ophthalmology Services (SEMOF) between September 2021 and September 2022. The local Committee of Ethics in Research approved this study. All patients were older than 18 years and fulfilled the updated American College of Rheumatology criteria for the diagnosis of SLE.[2] We excluded patients with a clinicaldiagnosis of any other rheumatologic disease (except secondary Sjögren's syndrome), a medical history of HIV or HTLV infection, severe hypertension, diabetes mellitus, and individuals with other ophthalmologic pathologies unrelated to systemic lupuserythematosus (SLE).

All patients underwent Schirmer test without anesthetics, break-up time test (TBUT), fluorescein and lissamine staining. All testes were done by the same ophthalmologist. Sicca symptoms were evaluated by the OSDI (Ocular Surface Disease Index) that is a questionnaire used to quantify the symptoms of patients with dry eye. It consists of 12 questions that are graded from 0 to 4. The final score can range from 0 to 100, with highervalues indicating more symptoms. It is validated for Brazilian-Portuguese language.[3]

The patients underwent clinical consultation and rheumatological physical examination. A blood sample was collected to determine the presence of autoantibodies (ANA, anti- SSA, anti-SSB, anti-DNA, anti-Sm and anticardiolipin). Disease activity was assessed using the SLEDAI-2K instrument,[4] and we adopted the following criteria:

- Inactive (SLEDAI-2K = 0);
- Low disease activity (SLEDAI-2K < 4);
- Moderate to high disease activity (SLEDAI-2K ≥ 4).

The Shirmmer-I test was considered negative or normal when the values were equal to orgreater than 10mm of filter paper wetting in 5 minutes, at the temporal lower eyelid margin, in each eye.[5] For the TBUT, we used 1% Fluorescein in the lower fornix, andit was considered positive or abnormal when the average of 3 consecutive measurements was less than 10 seconds. Surface staining was considered positive or abnormal when > 5 points stained on the cornea with fluorescein or > 9 points stained on the conjunctiva with lissamine green.[6] Presence of symptoms (OSDI ≥13) and at least one positive result from the evaluated homeostasis markers were considered as a diagnosis of Dry EyeDisease.

Statistical analysis

The statistical analysis was performed using the Statistical Package for the SocialSciences (SPSS, Chicago, IL, version 20). Descriptive data were presented in tables and expressed as frequency (n) and percentage (%) for categorical variables, and mean and standard deviation (SD) or median and interquartile range (IQR) for numerical data. Thet-test or Mann-Whitney test was used to compare means after testing the normality of quantitative variables. Normality was assessed using the Kolmogorov-Smirnov test. Correlation between variables was tested using Pearson's correlation or Spearman's correlation depending on the normality of the variables. A 95% confidence interval (CI) was used to estimate the precision of the findings. A p-value of <0.05 was considered statistically significant for all tests.

Results

Description of studied sample

A total of 114 patients (228 eyes) were enrolled in this study. Epidemiological, clinical, serological and treatment data of studied sample are summarized on Table 1. In this sample the median SLEDAI was 4,01 (range from 0-22). The Schirmer I test went from 0 to 35 mmm in both eyes (mean of 10,14 mm). The test was positive in at least one eye in 54.82%. The mean values of Tear Film Break-Up Time (TBUT) were 6.7±2.2 seconds (95% CI 6.4 to 7 seconds). The mean value of Lissamine Green staining was 1.7±1.9 (95% CI 1.4 to 1.9), and with fluorescein it was 1.5±1.6 (95% CI 1.2 to 1.7). The median OSDI was 16.66 (range from 0-79,54). Taking into consideration that for the diagnosis of dry eye, the patient should present symptoms (OSDI≥ 13) and at least one positive result from the evaluated homeostasis markers, we found that 53 patients (46.5%, 95% CI 37.5 to 55.7%) met the criteria adopted by us. We found an association between the presence of dry eye and positivity for anti-SSB (p=0.010) as well as with older age (p=0.024), but there was no associationwith the other tested variables (Table 2).

Table 1 Clinical, epidemiological and serological profile of studied sample

Variables	N = 114
	Mean (SD)
Age (years)	41,59 (11,45)
Disease duration (years)	11,38 (8,14)
Age at disease onset (years)	30,35 (10,57)
SLEDAI	4,01 (4,93)
C3 mg/dl	91,18 (29,56)
C4 mg/dl	19,96 (9,76)
	N (%)
Female gender	109 (95,6)
Hypertention	51 (44,7)
Nephritis	15 (13,2)
Glaucoma	3 (2,6)
Jaccoud's Arthropathy	24 (21,8)
ANA (N=88)	72 (81,8)
Anti-DNA (N=103)	28 (27,2)
Anti-SM (N=89)	25 (28,1)
Anti-SSA (N=90)	43 (47,8)
Anti-SSB (N=88)	12 (13,6)
Anti-RNP (N=87)	28 (32,2)
Anti-cardiolipin (N=90)	18 (20)
Predinisone users	50 (43,9)
Methotrexate users	23 (20,2)
Azathioprine users	36 (31,6)
Cyclosporine users	5 (4,4)
Mycophenolate mofetil users	4 (3,5)
Thalidomide users	1 (0,9)
Dapsone users	2 (1,8)
Cyclophosphamide users	1 (0,9)
Belimumab users	6 (5,3)

SD, standard deviation; SLEDAI, systemic lupus erythematosus disease activity index; N, sample size

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Table 2 Association of dry eye presence with clinical and laboratory variables

Variables	Dry Eye		
	No	Yes	P-value
Disease duration (years)	9(4-15,5)	13 (5,5-20)	0,107*
Dosage of Hydroxychloroquine	400 (285-400)	400 (285-400)	0,424*
C3	90,3±29,2	92,2±30,2	0,749**
C4	20,0±9,5	19,9±10,1	0,963**
Age	39,3±11,8	44,2±10,5	0,024**
SLEDAI			0,232***
Inactive	19 (34,5)	12 (24,5)	
Low disease activity	17 (30,9)	12 (24,5)	
activity	19 (34,5)	25 (51,0)	
ANA			0,841***
Non-reactive	8 (17,4)	8 (19,0)	
Reagent	38 (82,6)	34 (81,0)	
Anti-SSA			0,680***
Non-reactive	25 (54,3)	22 (50,0)	
Reagent	21 (45,7)	22 (50,0)	
Anti-SSB			0,010***
Non-reactive	43 (95,6)	33 (76,7)	
Reagent	2 (4,4)	10 (23,3)	
Anti-DNA			0,456***
Non-reactive	41 (75,9)	34 (69,4)	
Reagent	13 (24,1)	15 (30,6)	
Anti-Sm			0,365***
Non-reactive	35 (76,1)	29 (67,4)	
Reagent	11 (23,9)	14 (32,6)	
Anticardioplina			0,343***
Non-reactive	35 (76,1)	37 (84,1)	
Reagent	11 (23,9)	7 (15,9)	
Anti RNP		0,825***	
Non-reactive	31 (68,9)	28 (66,7)	
Reagent	14 (31,1)	14 (33,3)	
Duration of		0,490***	
hydroxychloroquine use			
Up to 5 years	31 (51,7)	23 (45,1)	
More than 5 years	29 (48,3)	28 (54,9)	
Nephritis		0,569***	
Yes	7 (11,5)	8 (15,1)	
No	54 (88,5)	45 (84,9)	

*Mann-Whitney test; **Independent t-test; ***Chi-square test

SLEDAI, systemic lupus erythematosus disease activity index; ANA, antinuclear antibody; Anti-Sm,anti-Smith antibody; Anti-SSA, anti-Sjögren's syndrome-related antigen A autoantibodies;Anti-SSB, anti-Sjögren's syndrome-related antigen B autoantibodies;Anti-RNP, antibody against the nuclear fraction of ribonucleoproteins; SD, standard deviation; N, sample size.

Discussion

Dry eye is the main ophthalmic manifestation in SLE (Systemic Lupus Erythematosus). Different studies have reported a wide range of prevalence for dry eye disease (DED) in patients with SLE, ranging from 0% to 32%. This variability can be attributed to factors such as variations in age, geographic locations, gender, racial groups, disease duration, severity, activity, and treatment regimens among participants in different studies.[1] Additionally, the lack of standardization for diagnosis leads to highly variable data amongstudies.

In a recent systematic review, Wang et al. (1) described the prevalence of dry eye in patients with SLE and found an estimate of 16% (95% CI 10 to 21%, p<0.001),considering the criteria proposed by the Japanese Society of Dry Eye in 1995. In anothercross-sectional study with lupus patients, where the diagnosis of dry eye was establishedby the positivity of the Schirmer I test, the prevalence of dry eye was estimated at 51.4%[7]

In our study, dry eye syndrome has a high prevalence, affecting approximately 46.5% ofthe patients. We found an association between the presence of dry eye and positivity for anti-SSB antibodies and older age. We did not find an association with disease activity. Itis important to consider that women consistently exhibited a higher prevalence of dry eyecompared to men in all studies stratified by sex.[8] Additionally, hormonal factors relatedto advanced age are known to influence the

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presence of dry eye.[9] Our population is predominantly female and in the peri-menopausal age group, which may have influencedour results. It is worth noting that many of our dry eye patients may have been carriers of secondary Sjogren's syndrome. Although characterizing such a syndrome is not the purpose of this study, the presence of anti-SSA/Ro antibodies in 46.7% of the sample studied reinforcesthis possibility. Of note, anti-SSB/La antibodies were observed in 23.3% of dry eye patients and only 4.4% of those without this complication.

Conclusion

Dry eye is an important ocular manifestation in SLE and has a significant impact on patients' quality of life. In our study, we followed the latest recommendations for the diagnosis of dry eye (10). Standardization for diagnosis is essential to harmonize findingsacross different cohorts, enabling a better understanding of the condition and associated variables, and facilitating more targeted therapeutic approaches.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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