

Dry eye in systemic lupus erythematosus patients

Olho seco em pacientes com lúpus eritematoso sistêmico

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ABSTRACT

Objective: To study the association of dry eye with lupus disease activity and cumulative damage. To verify if epidemiological, treatment and autoantibody profile of SLE (systemic Lupus erythematosus) patients influence the presence of dry eye. **Methods:** We studied 70 SLE patients for the presence of dry eye by Schirmer test, disease activity by SLEDAI (SLE-Disease activity index) and cumulative damage by SLICC/ACR DI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index). Patients were also submitted to the OSDI (Ocular Surface Disease Index) questionnaire. Epidemiological and treatment data and autoantibody profile were extracted from the charts. **Results:** Dry eye by Schirmer test was present in 51.4% of the sample. No association of the presence of dry eye with SLEDAI and SLICC DI were found ($p = ns$). Subjective symptoms of dry eye measured by OSDI showed a modest correlation with SLEDAI (Spearman $\rho = 0.32$). Treatment profile did not influence in the presence of dry eye that was more common in older patients ($p < 0.0001$). Anti dsDNA had a negative association with the presence of positive Schirmer test ($p = 0.0008$). **Conclusions:** Dry eye detected by Schirmer test in SLE patients has no association with disease activity nor cumulative damage. Anti dsDNA seems to have a protective effect in this context.

Keywords: Systemic lupus erythematosus; Dry eye syndrome; Autoantibodies

RESUMO

Objetivos: Estudar a associação do olho seco com a atividade do lúpus eritematoso sistêmico (LES) e seus danos cumulativos. Verificar se o perfil epidemiológico, de tratamento e de auto anticorpos de pacientes com LES influencia a presença de olho seco. **Métodos:** Foram estudados 70 pacientes com LES para a presença de olho seco pelo teste de Schirmer, atividade da doença por SLEDAI (SLE Disease Activity Index) e dano cumulativo por SLICC/ACR DI (Clínicas Colaborativas Internacionais de Lúpus Eritematoso Sistêmico/American College of Rheumatology Damage Index). Os pacientes também foram submetidos ao questionário OSDI (índice de doenças da superfície ocular). Os dados epidemiológicos e de tratamento e o perfil de auto anticorpos foram extraídos dos prontuários. **Resultados:** Olho seco pelo teste de Schirmer esteve presente em 51,4% da amostra. Nenhuma associação da presença de olho seco com SLEDAI e SLICC/ACR DI foi encontrada ($p = ns$). Os sintomas subjetivos do olho seco medidos por OSDI mostraram uma correlação modesta com SLEDAI (Rho de Spearman = 0,32). O perfil do tratamento não influenciou na presença de olho seco que era mais comum em uns pacientes mais idosos ($p < 0, 1$). Anti dsDNA teve uma associação negativa com a presença de teste positivo de Schirmer ($p = 0, 8$). **Conclusões:** Olho seco detectado pelo teste de Schirmer em pacientes com LES não tem associação com atividade da doença nem dano cumulativo. Anti dsDNA parece ter um efeito protetor neste contexto.

Descritores: Lupus eritematoso sistêmico; Síndrome do olho seco; Autoanticorpos

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INTRODUCTION

Dry eye is one of the most common ophthalmologic disorders. They can cause ocular irritation, redness, itching, photosensitivity, visual blurring and mucous discharge, impairing the patient's quality of life.⁽¹⁾

In systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) the dry eye can be secondary to Sjögren's syndrome (SS) that is an autoimmune disorder that affects all exocrine glands, including those responsible for the tear production.⁽²⁾ Although SS and SLE are both immune mediated diseases,^(2,3) no studies suggesting that the inflammatory activity of one of this entity may influence in the activity of the other exist. In previous studies, done in rheumatoid arthritis (RA), it was not possible to link sicca findings with RA inflammatory activity.^(4,5) However, the pathophysiologic mechanisms of SLE and SS are more alike than those of RA and SS. SS and SLE are driven by the same cytokine pattern of inflammation^(6,7) and share some genetic association.⁽⁸⁾

Presently we studied a sample of lupus patients aiming to know if SLE disease activity or cumulative damage were linked to the presence of dry eye. We also looked for the influence of epidemiological and treatment variables and autoantibodies profile in the dry eyes prevalence.

METHODS

The local Committee of Ethics in Research approved this study; all participants were older than 18 years and signed consent. This is a cross sectional study that included a convenience sample of 70 SLE patients from a single Rheumatology center. All included patients fulfilled at least four classification criteria for SLE diagnosis from the American College of Rheumatology – 1997.⁽⁹⁾ We excluded patients with ophthalmologic complications such as scleritis, episcleritis, scleromalacia, those with prior eye surgery and contact lenses users or those taking medications such as antidepressants, anticholinergics, antihistamine, diuretics, etc, those with hepatitis C or HIV infection or prior irradiation of the head and neck.

Epidemiological (age, gender, age at disease onset, ethnic background and tobacco use), clinical findings following the definition of 1997 ACR classification criteria for SLE,⁽⁹⁾ serological data [anti dsDNA, anti Ro/SS-A; anti La/SS-B, anti-RNP, anti-Sm, aCl (anticardiolipin) IgG, aCl IgM, LA (or lupus anticoagulant), rheumatoid factor and direct Coombs] were extracted from the charts. At our institution anti Ro/SS-A, anti La/SS-B, anti RNP, anti Sm, aCl IgG, aCl IgM were done by ELISA (using ALKA and Orgentec Kits[®]), anti dsDNA is done by immunofluorescence technique (IFT) using Crithidia luciliae as a substrate. Lupus anticoagulant is searched through a screening test, the dRVVT (dilute Russell viper venom test), and mixing patient's plasma with normal plasma and confirmed by RVVT. The direct Coombs or direct antiglobulin test were performed using monoclonal anti human globulin Fresenius-Kabi-Brasil[®].

All included patients had Schirmer test without anesthetics done according to standard recommendations⁽¹⁰⁾ and we considered a patient to be with definitive dry eye when values were equal or under 5 mm in at least one eye. All testes were done by a single examiner. For statistical purposes the value of the worst Schirmer was used. Simultaneously, the patients had disease activity measured by SLEDAI (SLE-Disease Activity index)⁽¹¹⁾ and cumulative damage measured by SLICC/ACR DI

(Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus).⁽¹²⁾ Sicca symptoms were evaluated by the OSDI (Ocular Surface Disease Index).⁽¹³⁾

The SLEDAI is an instrument to measure disease activity that takes into account clinical and laboratory findings in the past 10 days and has a range from zero to 105 where zero means no activity and 105 the most severe flare.⁽¹¹⁾

The SLICC/ACR DI instrument measures irreversible damage caused by the SLE or its treatment. Recorded items should have been present for at least 6 months. It goes from zero to 49; zero being the best scenario and 49, the worst.⁽¹²⁾

The OSDI measures how quality of life can be affected by dry eyes. It has 12 questions and it is graded from zero (no symptoms) to 100 (worst scenario) and it is validated for Brazilian-Portuguese language.⁽¹³⁾ Data were grouped in contingency and frequency table. Data distribution was suited by Shapiro-Wilk normality test. Central tendency of parametric samples were expressed in means and standard deviation (SD); in non-parametric, by median and interquartile range (IQR). To compare nominal data, we used the Fisher and chi-squared tests; for numerical data, we used the unpaired t and Mann-Whitney tests. Correlation studies were done by Spearman test. The significance adopted was 5%.

RESULTS

Description of studied sample

Epidemiological, clinical, serological and treatment data of studied sample are summarized on Table 1.

In this sample the median SLEDAI was 2.0 (range from 0-12) and the median SLICC was 2.0 (range from 0 to 10).

The Schirmer test went from 0 to 35 mm in both eyes (mean of 7 mm in the right eye and of 10 mm in the left eye). The test was positive in at least one eye in 36/70 of them (51.4%). The median OSDI was 16.04 (range from 0-100).

Comparison of SLE population with at least one dry eye with those without it

The comparison of clinical, serological, activity data and data on cumulative damage in patients with and without at least one dry eye is on Table 2. In this table, it is possible to note the protective effect of anti-dsDNA as well as the lack of association of objective dry eye with disease activity, cumulative damage and subjective symptoms. Older individuals had higher prevalence of dry eye.

Neither the presence of tobacco exposure nor any of the used medication were associated with the presence of positive Schirmer test (all p=ns).

Correlation studies of OSDI with Schirmer values showed p=0.71 (rho=-0.04; 95% CI=-0.28 to 0.19); with SLEDAI, p=0.005 (rho=0.32; 95% CI=0.09-0.52) and with SLICC, p=0.05 (rho=0.23; 95% CI=-0.008 to 0.44).

DISCUSSION

The presence of at least one dry eye in our sample was quite high involving almost half of the studied lupus sample. Our results showed also that, in this population, no association of objective dry eye with lupus activity neither with lupus cumulative index was found. However, the presence of anti-dsDNA seems to have a protective role. Interestingly, a dissociation between objective signs and the subjective feeling of dryness and a positive correlation of dry eyes symptoms with disease activity was detected.

Table 1
Clinical, epidemiological and serological profile of studied sample of 70 systemic lupus patients

	N or range	% or central tendency
Female gender	64/70	91.4%
Age (years)	18-70	Mean 43.5±12.6
Age at disease onset (years)	17-58	Median 30.0 (IQR=23.0-41.0)
Ethnic background	Caucasians– 40/70	Caucasians – 57.1%
	Afro descendants –30/70	Afrodescendants-42.8%
Tobacco exposure	No - 48/70	No - 68.5%
	Exposed (ex and current smokers)= 22/70	Exposed =31.4%
Disease duration (years)	0.16 a 36	Median 10.0 (IQR=5.0-16.2)
Acute skin lesions	36/70	51.4%
Chronic skin lesions	26/70	37.1%
Mucosal ulcers	35/70	50%
Alopecia	45/70	64.2%
Arthritis	51/70	72.8%
Serositis	22/70	31.4%
Glomerulonephritis	34/70	49%
Hemolytic anemia	14/70	20%
Leukopenia	30/70	42.8%
Thrombocitopenia	14/70	20%
Neurological involvement	15/70	21.4%
Anti-dsDNA	32/40	45.7%
Anti-Sm	23/70	32.8%
Direct Coombs	14/70	20%
Anti-Ro	28/70	40%
Anti-La	10/69	14.4%
Anti-cardiolipin Ig G	11/70	15.7%
Anti-cardiolipin IgM	9/70	12.8%
Lupus anticoagulante	9/70	12.8%
Prednisone users	28/70	40%
Mean prednisone (mg/day)	0-60	Median 0 (IQR=0-5.0)
Methotrexate users	10/70	14.2%
Mophetil mycophenolate users	19/70	27.1%
Antimalarial users	60/70	85.7%
Azathioprine users	9/70	11.4%

IQR= interquartile range.

Table 2
Comparison of systemic lupus erythematosus patients with and without at least one dry eye according to the Schirmer's Test

	With at least 1 dry eye n=36	Without dry eye N=34	p-value
Median age (years) (IQR)	43.5 (38.0-57.7)	29.0 (22.0-40.2)	< 0.0001
Median age at disease onset (years) (IQR)	33.5 (25.2-42.5)	29.0 (22.0-40.2)	0.13
Median SLEDAI (IQR)	2 (0-4)	2.0 (0-6)	0.75
Median OSDI (IQR)	14.6 (2.1-40.0)	17.8 (3.7-35.3)	0.82
Anti-Ro	11/36 (30.5%)	17/34 (50%)	0.09
Anti-La	3/36 (8.3%)	7/33 (21.2%)	0.17
Anti-cardiolipin IgG	6/36 (16.6%)	5/34 (14.7%)	1.00
Anti-cardiolipin IgM	3/36 (8.3%)	6/34 (17.6%)	0.29
Lupus anticoagulante	5/36 (13.8%)	4/34 (11.7%)	1.00
Anti-dsDNA	11/36 (30.5%)	21/34 (61.7%)	0.008 (*)
Anti-Sm	13/36 (36.1%)	10/34 (29.4%)	0.55

(*)-OR=3.67 (1.36-9.88);

IQR= interquartile range; OSDI= Ocular surface disease index; SLEDAI = SLE disease activity index; SLICC = SLE cumulative damage index.

Dry eye or ceratoconjunctivitis sicca is the commonest eye manifestation in SLE and, according to the literature is found in almost one third of them,⁽¹⁴⁾ a number that was lower than that found presently. Others have described values from 25 to 36% while studying Sjögren prevalence in SLE.^(15,16) As we did not study Sjögren's syndrome, but only dry eye, environmental variables may have had influence in our findings. Differences in the genetic background of studied sample may also account for such results, as SS has genetic predisposition.⁽⁷⁾

Studying the association between SLE and SS, Baer et al.⁽¹⁷⁾ noted that the SLE diagnosis came before the SS diagnosis more frequently. In their study, the authors showed that SLE patients with SS were older at disease onset than those without SS. On the other hand, McDonagh et al.⁽¹⁸⁾ studying retrospectively 215 SLE patients found that lupus patients associated with other autoimmune disease, such as Sjögren, were younger. We could not find any differences in age at SLE diagnosis but an association of dry eye with age itself was noted. Hormonal factors, secondary to higher age and known to influence the presence of dry eye, may have played a role in this context.⁽¹⁹⁾

Concerning tobacco exposure, 31.4% of our patients had a positive finding. Previous studies are divergent on this data. Smoking may result in increased lacrimal osmolarity, impairing eye lubrication and causing damage to the ocular surface.⁽²⁰⁾ However, Olsson et al.,⁽²¹⁾ analyzing patients with primary Sjögren's syndrome found that smoking had a protective role, as happens in another autoimmune disease, such as ulcerative colitis. In our study, no association (neither positive nor negative) of dry eye with tobacco exposure was obtained.

Finally, a negative association of the anti-dsDNA presence with dry eye was seen in this study. This result is opposite of those of Chen et al.⁽²²⁾ that found a positive association. These authors postulated that the dsDNA could infiltrate the lacrimal apparatus causing destruction and dryness. Nevertheless, it is worthwhile to note that these autoantibodies are heterogeneous and some of them have been found not to be pathogenic.⁽²³⁾ In addition, the presence of anti-dsDNA may fluctuate according to the lupus activity.⁽²³⁾ and our population had a quite low level of activity (with median SLEDAI of 2). More studies, to understand the real value of this finding, are needed.

CONCLUSION

Summarizing, in our study we found a high prevalence of dry eye in lupus patients. No association of this finding with SLE disease activity and cumulative damage could be established. A negative association of dry eye presence with anti-dsDNA was verified.

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ERRATA

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