PAPER

Ocular involvement in systemic lupus erythematosus patients: a paradigm shift based on the experience of a tertiary referral center

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Objective: To evaluate ocular involvement in a cohort of systemic lupus erythematosus (SLE) patients of a tertiary referral center and to compare the results with the existing literature. **Methods:** Patients underwent a complete ophthalmological evaluation, including visual acuity, slit-lamp examination, fluorescein staining, Schirmer-I test, Goldmann applanation tonometry, funduscopy, 10-2 automated threshold visual fields, fundus autofluorescence and spectral-domain optical coherence tomography to screen for hydroxychloroquine (HCQ) macular toxicity. **Results:** A total of 161 patients (16 men and 145 women) were enrolled in this study. The mean age was 47.6 years and the mean disease duration was 11.5 years. Fifty patients (31.1%) had at least one ocular manifestation of SLE. The most frequent manifestation was dry eye syndrome (12.4%), immediately followed by cataracts (11.2%) and HCQ macular toxicity (11.2%). Among patients with HCQ maculopathy, two presented with an atypical spectral-domain optical coherence tomography pattern. Five patients (3.1%) presented with glaucoma, two patients (1.2%) presented with SLE retinopathy while only one presented with lupus choroidopathy (0.6%). **Conclusions:** Compared with previous studies, we conclude there has been a significant reduction in disease-related ocular complications, particularly those associated with poor systemic disease control. On the other hand, drug and age-related complications are assuming a prominent role in the ophthalmic care of these patients. *Lupus* (2020) 29, 283–289.

Key words: Glucocorticoids; hydroxychloroquine; maculopathy; ocular manifestations; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease that can involve any organ system. Ocular involvement occurs in approximately one third of SLE patients and virtually any ocular structure can be affected. Keratoconjunctivitis sicca is the most frequent ophthalmic complication, affecting nearly 33%,

frequently associated with secondary Sjogren's syndrome.¹ Posterior segment involvement, namely lupus retinopathy, choroidopathy and optic neuropathy is particularly concerning given their potential for a devastating impact on visual prognosis and their relation with poor systemic disease control.² According to most reports, lupus retinopathy is the second most common ocular manifestation with an incidence that may reach 29%.³ However, over the last few years we have been entering a new era in the treatment of SLE. Biologic agents have entered the therapeutic armamentarium, and anti-malarials, particularly hydroxychloroquine (HCQ), have been introduced as long-term maintenance therapy to almost every patient early in the course

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of the disease.⁴ Consequently, there has been a significant improvement in systemic disease control, a reduction in lupus flares, with a marked decrease in morbidity and mortality. As a result of these advances, changes in ophthalmic manifestations are expected, with a reduction in disease-related complications and an increase in age-related complications as well as an increase in drug-related ocular toxicity.

The objective of this study was to evaluate ocular involvement in a cohort of SLE patients of a tertiary referral center and to compare the results with the existing literature.

Materials and methods

This prospective study was conducted at the Ophthalmology Department of Central Lisbon Hospital and University Center between July 2017 and July 2019. SLE patients were sent for ophthalmological evaluation by the Autoimmune Disease Unit of the hospital, which is a tertiary referral center for SLE. All patients fulfilled the updated American College of Rheumatology criteria for the diagnosis of SLE.⁵ Patients underwent a complete ophthalmological evaluation that included best corrected visual acuity, slit-lamp examination, Goldmann applanation tonometry, Schirmer-I test with topical anesthesia, fluorescein staining and funduscopy under pharmacological mydriasis. In patients currently or previously medicated with HCQ, 10-2 automated threshold visual fields, fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT) were performed to screen for macular toxicity. To those in whom macular toxicity was suspected based on the above-mentioned examinations, multifocal electroretinogram (mfERG) was also performed. Toxicity diagnosis required an abnormal visual field examination confirmed by at least one of the above-mentioned objective examinations, according to the American Academy of Ophthalmology guidelines.⁶ Patients were then divided in two groups according to the presence or absence of HCQ maculopathy and a comparison of the clinical characteristics between groups was performed. This study was approved by our Institutional Ethics Committee and written informed consent was obtained from all participants. The tenets of the Declaration of Helsinki were followed.

Statistical analysis

Qualitative data were presented as frequencies (percentages) and quantitative data as means (standard deviation). Prevalence was presented with 95% confidence intervals. Normality of the variables was verified using the Shapiro–Wilk test and the difference between groups was tested by chi-square and the Student's *t*-test. A level of significance $\alpha = 0.05$ was considered. Data were analyzed using the Statistical Package for the Social Sciences for Windows (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and OpenEpi (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version www.OpenEpi.com, updated 06/04/2013, accessed 22/10/2019).

Results

A total of 161 patients (16 [9.9%] men and 145 [90.1%] women) were enrolled in this study. The mean age was 47.6 (standard deviation: 13.4) years and the mean disease duration was 11.5 (standard deviation: 5.1) years. Sixty-six patients (41.0%) had at least one sign of ophthalmic disease; however, when we considered only those manifestations directly related to the disease or its therapy (dry eye syndrome, cataracts, HCQ toxicity, glaucoma, lupus retinopathy or choroidopathy and uveitis), this number dropped to 50 patients (31.1%). Among ophthalmic manifestations, the most frequent was dry eye syndrome, followed by cataracts or previous cataract surgery (Table 1). Regarding medication with HCQ, 130 (80.7%) patients were currently medicated with this drug, 27 (16.8%) had been treated with it previously but had discontinued and four (2.5%) patients were treatment naïve at the time of the evaluation. Eighteen (11.2%) patients met the criteria for HCQ macular toxicity. Among the patients with HCQ maculopathy, one patient had classic bull's eye maculopathy (Figure 1), one had cystoid macular degeneration (Figure 2) and one had pigment epithelial detachment, which spontaneously resolved 6 months after discontinuing the drug (Figure 3). The remaining 15 patients had classic parafoveal photoreceptor layer thinning with corresponding visual field defects (Figure 4). Only the patient with bull's eye maculopathy complained of decreased visual acuity, the remaining were asymptomatic.

In Table 2 we compare SLE patients with and without HCQ maculopathy. Patients with macular toxicity were significantly older than those without this complication ($p=0.014$). Additionally, there was a statistically significant difference between these two groups regarding HCQ cumulative dosage ($p<0.001$) and treatment time ($p<0.001$), which were higher in the group with macular toxicity. HCQ was discontinued in all patients meeting the

criteria of macular toxicity. Good systemic disease control allowed, in most cases, a simple withdrawal of HCQ. In only two cases was azathioprine dosage increased in order to solve disease exacerbation.

Discussion

In this study, which included 161 SLE patients, disease-related ocular manifestations were present in 31.1% of patients, a proportion that is in line with previous studies.^{7,8} However, the relative frequency of each ophthalmic manifestation has changed compared with past studies. There has been an increase in drug and age-related manifestations and a decrease in disease-related ocular complications, particularly those directly linked to systemic disease activity. To our knowledge, this is the first epidemiologic study on ophthalmic manifestations of SLE performed in Portugal.

Dry eye syndrome was the most common form of ocular involvement in this cohort, with a prevalence of 12.4%, which is in line with previous reports.^{9,7} However, the proportion of patients with lupus retinopathy has significantly decreased compared with past studies. It was previously reported as the second most common ocular complication, with a prevalence of 7–29%.¹⁰ In our study, only 1.2% of patients presented with this

Table 1 Prevalence of ocular disease in SLE patients

Ocular abnormalities	Frequency	% (95% confidence interval)
Dry eye syndrome	20	12.4 (8.2–18.4)
Cataract or previous cataract surgery	18	11.2 (7.2–17.0)
Hydroxychloroquine retinopathy	18	11.2 (7.2–17.0)
High myopia	7	4.3 (2.1–8.7)
Glaucoma	5	3.1 (1.3–7.1)
Amblyopia	4	2.5 (1.0–6.2)
Strabismus	3	1.9 (0.6–5.3)
Lupus retinopathy	2	1.2 (0.3–4.4)
Macular epiretinal membrane	2	1.2 (0.3–4.4)
Lupus choroidopathy	1	0.6 (0.1–3.4)
Pterygium	1	0.6 (0.1–3.4)
Conjunctival intraepithelial neoplasia	1	0.6 (0.1–3.4)
Anterior uveitis	1	0.6 (0.1–3.4)
Fuchs endothelial dystrophy	1	0.6 (0.1–3.4)
Bilateral Coloboma	1	0.6 (0.1–3.4)
Choroidal nevus	1	0.6 (0.1–3.4)

Figure 1 Fundus autofluorescence (A and C), macular visual field results (B and D) and spectral-domain optical coherence tomography (E and F) of a 42-year-old male patient with bull's eye maculopathy. Yellow arrows point out the central ring of reduced autofluorescence, corresponding to advanced retinal pigment epithelium loss. The yellow marks on optical coherence tomography images highlight the central area of outer retinal damage, with marked disruption of photoreceptors and retinal pigment epithelium layers.

Figure 2 Spectral-domain optical coherence tomography of a 69-year-old patient with unilateral macular cystoid degeneration (yellow arrow).

Figure 3 Spectral-domain optical coherence tomography of a 48-year-old female on hydroxychloroquine therapy for 20 years showing unilateral pigment epithelial detachment (a) (yellow arrow). Six months after stopping the drug, the pigment epithelial detachment resolved spontaneously (b).

Figure 4 Fundus autofluorescence (a and c) and spectral-domain optical coherence tomography (b and d) of a 45-year-old female treated with hydroxychloroquine for 16 years. The arrows point out an area of increased autofluorescence in a bull's eye pattern. The arrow heads in the optical coherence tomography images delineate the paracentral thinning of the photoreceptors' layer.

Table 2 Comparison between SLE patients with and without hydroxychloroquine macular toxicity

Variables	With macular toxicity (n = 18)	Without macular toxicity (n = 143)	p-value
Age (years)	54.9 (11.2)	46.7 (13.4)	0.014
Male/female ratio	1/9	1/10.4	0.860*
HCQ cumulative dosage (g)	2130.1 (1341.6)	939 (893.5)	<0.001
HCQ treatment time (years)	14.7 (9.6)	6.9 (6.4)	<0.001

Results are expressed as mean (standard deviation), except for male/female ratio. *Chi-square test, remaining p-values were obtained by Student's t-test.

HCQ = hydroxychloroquine.

complication. Lupus retinopathy is a potentially sight-threatening complication that may manifest as retinal microangiopathy, retinal vasculitis or severe arterial or venous vaso-occlusion.² Lupus choroidopathy is another sight-threatening manifestation that can occur in isolation or associated with lupus retinopathy. It may present with single or multiple areas of serous retinal detachment, retinal pigment epitheliopathy, retinal pigment epithelium (RPE) detachment, choroidal ischemia or effusion.^{11,8} In our cohort, it was observed in

0.6% of the patients, which also represents a slight decrease compared with previous studies.^{11,2} Moreover, lupus retinopathy and choroidopathy reflect high systemic disease activity and significantly correlate with central nervous system lupus and renal involvement, being a negative prognostic marker for survival.^{12,13} Over the last decade, significant improvements in the medical management of SLE have occurred, which have led to better systemic disease control as well as to a reduction in morbidity and mortality. The significant

reduction in lupus retinopathy and choroidopathy is a direct consequence of the improvement in the standard of care of SLE.

Antimalarials, particularly HCQ, are nowadays the cornerstone of SLE medical therapy. Chronic medication with HCQ has proven beneficial in reducing lupus flares, end-organ damage and increasing survival rates in these patients.^{14,15} However, this benefit comes with a cost. Earlier studies reported an HCQ toxicity prevalence of 0–4%.¹⁶ However, the widespread use of these drugs for longer periods, with higher cumulative dosages and improvements in the screening strategy over recent years, have led to an increase in these estimates to 7.5–13.1%.^{17,18} In our study, 11.2% of patients presented with HCQ macular toxicity, which is consistent with these later studies. The subgroup of patients with HCQ toxicity was a high-risk group, with a mean treatment time of approximately 15 years and a cumulative dosage of approximately 2130 g. The pattern of HCQ retinal toxicity in clinical practice has also changed. In the past, the typical clinical picture was the classic bull's eye maculopathy with a paracentral ring scotoma, as a consequence of a paracentral ring of RPE atrophy. These defects were irreversible and often progressive, even after discontinuing the drug.¹⁹ Nowadays, modern screening methods, including SD-OCT, macular automated threshold visual fields, FAF, and mfERG, allow us to detect early paracentral photoreceptor damage, before the RPE affection takes place.⁶ Atypical patterns of maculopathy, such as cystoid macular degeneration or RPE detachment, like those observed in our cohort, have already been described.^{20,21}

Another interesting finding in our study was the relative increase in the diagnosis of cataracts and glaucoma (11.2% and 3.1% respectively). These numbers supersede those of earlier literature but are consistent with a more recent study, by Carli *et al.* that reported cataracts in 29% of patients and glaucoma in 3% of cases.^{7,22} This tendency for an increase in the diagnosis of cataracts and glaucoma in SLE patients is related to chronic corticosteroid therapy, as there is an association between cumulative corticosteroid dosage and the incidence of these complications.²² Age is another important risk factor for both glaucoma and cataracts. Given the significant improvements in medical management of SLE, these patients tend to live longer and thus additionally suffer the effects of age-related ophthalmic diseases.

In conclusion, there has been a paradigm shift in ocular involvement in SLE patients. We observed a significant reduction in ophthalmic complications

directly related to systemic disease activity, particularly lupus retinopathy. On the other hand, there has been an increase in drug and age-related ocular complications, such as HCQ maculopathy, cataracts and glaucoma. These phenomena are a consequence of improvements in the treatment of SLE and the associated increase in life expectancy of these patients. These results highlight the importance of regular ophthalmic screening, even in asymptomatic and systemically controlled SLE patients.

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References

- 1 Jensen J, Bergem H, Gilboe I, Husby G, Axéll T. Oral and ocular sicca symptoms and findings are prevalent in systemic lupus erythematosus. *J Oral Pathol Med* 1999; 28: 317–322.
- 2 Dias-Santos A, Proença RP, Tavares Ferreira J, *et al.* The role of ophthalmic imaging in central nervous system degeneration in systemic lupus erythematosus. *Autoimmun Rev* 2018; 17: 617–624.
- 3 Davies JB, Rao PK. Ocular manifestations of systemic lupus erythematosus. *Curr Opin Ophthalmol* 2008; 19: 512–518.
- 4 Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. *Intern Med J* 2012; 42: 968–78.
- 5 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
- 6 Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016; 123: 1386–1394.
- 7 El-Shereef RR, Mohamed AS, Hamdy L. Ocular manifestation of systemic lupus erythematosus. *Rheumatol Int* 2013; 33: 1637–1642.

- 8 Silpa-Archa S, Lee JJ, Foster CS. Ocular manifestations in systemic lupus erythematosus. *Br J Ophthalmol* 2016; 100: 135–141.
- 9 Pasoto SG, Martins VA de O, Bonfa E. Sjögren's syndrome and systemic lupus erythematosus: links and risks. *Open Access Rheumatol Res Rev* 2019; 29: 33–45.
- 10 Conigliaro P, Cesareo M, Chimenti MS, et al. Take a look at the eyes in Systemic Lupus Erythematosus: A novel point of view. *Autoimmun Rev* 2019; 247–254.
- 11 Nguyen QD, Uy HS, Akpek EK, Harper SL, Zacks DN, Foster CS. Choroidopathy of systemic lupus erythematosus. *Lupus* 2000; 9: 288–298.
- 12 Stafford-Brady FJ, Urowitz MB, Gladman DD, Easterbrook M. Lupus retinopathy. Patterns, associations, and prognosis. *Arthritis Rheum* 1988; 31: 1105–1110.
- 13 Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, Stevens MB. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 1986; 104: 558–563.
- 14 Durcan L, Petri M. Immunomodulators in SLE: clinical evidence and immunologic actions. *J Autoimmun* 2016; 74: 73–84.
- 15 Shinjo SK, Bonfá E, Wojdyla D, et al. Antimalarial treatment may have a time-dependent effect on lupus survival: data from a multinational Latin American inception cohort. *Arthritis Rheum* 2010; 62: 855–862.
- 16 Marmor MF, Kellner U, Lai TYY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 2011; 118: 415–422.
- 17 Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014; 132: 1453–1460.
- 18 Palma Sánchez D, Rubio Velazquez E, Soro Marín S. Retinal toxicity due to antimalarials: frequency and risk factors. *Reumatol Clin* 2013; 9: 259–262.
- 19 Marmor MF, Hu J. Effect of disease stage on progression of hydroxychloroquine retinopathy. *JAMA Ophthalmol* 2014; 132: 1105–1112.
- 20 Kellner S, Weinitz S, Farmand G, Kellner U. Cystoid macular oedema and epiretinal membrane formation during progression of chloroquine retinopathy after drug cessation. *Br J Ophthalmol* 2014; 98: 200–206.
- 21 Lee WJ, Ko MK, Lee BR. Hydroxychloroquine retinopathy combined with retinal pigment epithelium detachment. *Cutan Ocul Toxicol* 2012; 31: 144–147.
- 22 Carli L, Tani C, Querci F, et al. Analysis of the prevalence of cataracts and glaucoma in systemic lupus erythematosus and evaluation of the rheumatologists' practice for the monitoring of glucocorticoid eye toxicity. *Clin Rheumatol* 2013; 32: 1071–1073.

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