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Ocular manifestations of systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, multi-systemic autoimmune disease that can affect various parts of the body, including the eyes. Ocular findings are reported in about one-third of SLE patients and can be the initial manifestations of the disease, often complicated by going unnoticed. This study aimed to determine the frequency, pattern, and potential severity of ocular manifestations in SLE patients. A cross-sectional hospital-based study was conducted between January and June 2019 at the Lagos State University Teaching Hospital, involving 71 adult patients (aged 18 years and above) diagnosed with SLE. Data was collected using semi-structured and Standard Patient Evaluation for Dryness (SPEED) questionnaires, medical records, and comprehensive ocular examinations including visual acuity, slit-lamp examination, Tear Film Break-Up Time (TBUT), and Schirmer's test. Dry eye disease was defined as dysfunction of the tear film and ocular surface based on SPEED questionnaire symptoms, or abnormal Schirmer's test, or TBUT. Data was analysed using Stata statistics software version 13 (copyright Stata Corp LP, USA). The study population had a mean age of 38.7 years, with 94.37% being female. The most frequent ocular symptom reported was difficulty looking at light (44%). The most common ocular manifestations observed were dry eye disease (71.43% prevalence, using both TBUT and Schirmer's test criteria), cataract (15.49%), and maculopathy (18.31%). A significantly higher frequency of cataract was found in the older age group (48 to 74 years) compared to the younger age group (18 to 47 years) (47.06% vs. 5.56%, p-value < 0.001), with increasing age being a statistically significant predictor for cataract development (OR = 1.15, p<0.001). While participants with a cumulative hydroxychloroquine (HCQ) dose ≥1000 g had a slightly higher proportion of maculopathy (19%) compared to those with <1000 g (15%), this was not statistically significant (p=1.00). Increasing age was also a significant predictor for dry eye disease (OR=1.07, p=0.01). No statistically significant predictor was found for the severity of dry eye disease in this study. In conclusion, there is a high occurrence of ocular involvement in SLE patients, with dry eye disease being the most common manifestation. Cataract and maculopathy are also frequent findings, with the risk of cataract and dry eye increasing with age. Routine eye screening for SLE patients is recommended, particularly as the cumulative dosage of HCQ approaches 1000 g.

Keywords: Systemic lupus erythematous; Ocular manifestations; Dry eye disease; Cataract; Maculopathy.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-systemic, multi-factorial connective tissue disease with a genetic predisposition in which the body's immune system mistakenly attacks healthy tissues in different parts of the body, including the skin, joints, kidneys, brain and eyes [1]. The reported prevalence of SLE in developed countries is said to be 20–150 cases per 100,000 [2,3]. The highest prevalences were reported in Italy, Spain, and the United Kingdom-Afro-Caribbean population [4]. The hospital-based prevalence in a developing country such as Nigeria is about 2 to 5% [5-7]. The disease is particularly prevalent in adult females with a female-to-male ratio of 7:1. Among women, blacks have a higher prevalence of lupus by 2.5 to 3.5 fold compared to whites [2].

SLE can cause various health problems, and when it comes to the eyes, some of these problems (ocular findings) may go unnoticed at first, which further complicates its management. These ocular findings occur in about one-third of patients with SLE [9]. These may vary from patient to patient and can correlate with systemic disease activity [10]. Ocular manifestations in SLE are due to immune complex deposition in ocular tissues, particularly in the blood vessels of the conjunctiva, sclera, ciliary body, choroid, and retina [11,12]. The incidence, severity, and disease course of ocular features vary, with many factors contributing to the natural history of the disease, like gender, the underlying systemic disease, and the extent of the inflammatory process [12]. Findings may range from abnormalities of the ocular adnexa, keratoconjunctivitis sicca, iridocyclitis, scleritis, retinal vasculitis, vaso-occlusive disorder, and choroidopathy to optic neuropathy [10].

Features of SLE in the eye may be due to the disease or the complications of systemic or topical therapy [9]. It can affect any structure of the eye and adnexa, unlike other connective tissue diseases, which may have a predilection for either the anterior or posterior segment of the eye. Ocular findings are important as they may be the initial manifestation of the disease [9]. The eye, although not a primary target of immune-mediated damage in SLE, can be affected in a variety of ways, resulting in significant ocular morbidity [14]. This study aims to determine the frequency, pattern, and possibly severity of ocular manifestations in SLE patients attending the Rheumatology clinic of the Lagos State University Teaching Hospital.

Materials and methods

Study site

The study was carried out at the Lagos State University Teaching Hospital (LASUTH), Ikeja. This teaching hospital is one of the two tertiary centres serving the over 14 million inhabitants of Lagos State and its environs. The Rheumatology unit is one of the nine major units of this hospital. It provides high-quality, personalized patient care and leading-edge research programs with a dedicated clinic staffed by consultants, trainee rheumatologists, nurses, and facilitators. It runs a twice-weekly clinic that accommodates an average of ten (10) newly diagnosed and sixty (60) follow-up patients per week. Patients are often referred to the Ophthalmology clinic from the Rheumatology clinic for visual assessment.

Study design

This is a cross-sectional hospital-based study conducted between January and June 2019. Patients aged 18 years and above, diagnosed with SLE according to the American College of Rheumatology criteria, who provided written informed consent, without any other diagnosed connective tissue disease, without a history of malignancy or on chemotherapy, without any history of ophthalmic disease/injury/cosmetics use (e.g. contact lens) and not pregnant were recruited into the study.

Sample size estimation

The sample size was calculated using a single-proportion formula [15] based on the assumption of proportion (p=4%) of SLE patients in the hospital from previous studies [5-7], an absolute precision of 0.05, a 95% confidence level and an estimated 20% non-response rate, a total of 71 was obtained.

Sampling technique

Participants were recruited from the Rheumatology clinic twice weekly. All newly diagnosed and SLE patients on follow-up were interviewed to sort out those who met the eligibility criteria. At the interview, detailed study information was provided to the patients. Consecutive consenting patients with SLE who fulfilled the criteria were recruited. Medical records of consenting patients were retrieved for the collection of relevant information; additional information was obtained from the participants at the Ophthalmology clinic.

Ethical approval

Approval to conduct this study was obtained from the Lagos State University Teaching Hospital Medical and Health Research Ethics Committee, and the tenets of the Helsinki Declaration were strictly adhered to. Permission was also obtained from the Heads of the Department of Rheumatology and Ophthalmology Clinics. Written informed consent was obtained from all study participants.

Study procedure or data collection

Recruitment was done at the Rheumatology clinic where potential participants were provided with study information. Those who consented and met the eligibility criteria were recruited. Information was collected from participants via the semi-structured and Standard Patient Evaluation for Dryness (SPEED) questionnaires by trained study personnel. The patients were then accompanied to the Ophthalmology clinic which is less than a minute walk, where the ocular examination was done on the same day as the interview.

The study questionnaire consisted of 5 sections. Section 1 captured basic demographic data and some risk factors that might affect the severity of the ocular symptoms in SLE patients. Relevant past medical history and medication that the patient is currently on for the treatment of SLE were obtained in section 2. Section 3 captured significant ocular symptoms e.g. reduction in vision, red eyes, aversion to light, etc. In section 4, the laboratory results were retrieved from the hospital records of the patient. Lastly in section 5, all ocular examinations and tests conducted were recorded.

The SPEED questionnaire is a standardized dry eye questionnaire16 which assesses the frequency of ocular subjective symptoms (soreness, blurred vision), the severity of symptoms (tolerable, uncomfortable, and intolerable), and previous use of eye drops or ointment. It also monitors diurnal and long-term changes in symptoms over 3 months [17]. The patients answered 13 questions, with higher scores representing greater disability. The composite score of the SPEED questionnaire is obtained by summing the scores from the frequency and severity parts of the questionnaire. Summary scores of the frequency and severity questions of the SPEED questionnaire were derived by summing the 0 to 4 scores of each of the 8 questions, and the total was referred to as the "SPEED score" in the range of 0 to 28 [16]. The symptoms inquired by the SPEED questionnaire included dryness or grittiness or scratchiness, soreness or irritation, burning or watering and eye fatigue reported and scored as sometimes (1), often (2), and constant (3) and whether these symptoms pose no problems (0), were tolerable (1), uncomfortable (2), bothersome (3), or intolerable (4). The format of the SPEED questionnaire was modified for ease of data capturing but the contents remained the same.

Ocular examination

The ocular examination included assessing visual acuity using Snellen's chart for literate patients, E chart for non-literate patients with and without pinhole, near vision chart, Amsler's grid test at 33 cm, starting with the first chart and subsequently with others if the first chart was not interpreted adequately. The other charts are not tested if the first chart is interpreted adequately by the patient. Slit-lamp examination of both eyes was done first by using the broad beam of the Haag Streit slit lamp to assess the condition of the ocular surface and adnexa, particularly observing eyelids, tear film meniscus, conjunctiva for changes, evidence of episcleritis, scleritis and for cornea changes like loss of lustre, abrasions, ulcers, opacities. The anterior chamber was examined for evidence of flare, cells, iris was examined for nodules, and the pupil was examined for abnormalities such as irregularities, and evidence of posterior synechiae.

Tear film Break-Up Time (TBUT) and Schirmer's test I was also done to assess the quality and quantity of tears produced. These tests were performed on all participants under controlled room conditions in a semi-lit room and air conditioner or fan switched off. The TBUT test was assessed first (This is because the Schirmer test can disrupt tear film stability and cause false-positive ocular surface dye staining) and 10 minutes later, the Schirmer's test I test was performed on both eyes, starting with the right eye.

TBUT was measured by instilling a fluorescein strip moistened with a drop of water for injection into the inferior conjunctival fornix, the participant was instructed to blink 3 times and then hold the eyes open. The tear film was examined using the broad beam of cobalt blue light of the slit-lamp bio-microscope for the appearance of dark spots on the cornea representing areas of dryness. A stopwatch was activated when the patient stopped blinking and deactivated when the first random dark spot appeared. The time interval between the last blink and the appearance of the first dry spot around the central cornea was noted as the TBUT measurement and a value of less than 10 seconds was considered abnormal and indicative of dry eye. TBUT was repeated three times at 10-second intervals for each eye, and the average TBUT was recorded.

Schirmer's test I which measures maximum basic and reflex secretion was done using a 5 mm by 35 mm No. 41 Whatman's filter paper without prior instillation of topical anesthetic drops. The filter paper was folded 5 mm from one end and inserted midway between the outer and the middle third of the lower lid into the conjunctival fornix. The participant was asked to gently close the eyes. The paper was removed after 5 minutes and the amount of wetting was measured from the fold. A reading of less than 10 mm was regarded as abnormal and considered indicative of dry eye disease. For those on tear substitutes, TBUT and Schirmer's tests were performed after overnight discontinuation of their ocular medications. Intraocular pressure was measured with the Perkin's handheld applanation tonometer. Pupillary dilatation was done with 1% tropicamide for fundus examination. Clinical examination with direct and indirect ophthalmoscopes was done to assess the status of the optic nerve and retina, observing for evidence of optic neuropathy, maculopathy, vasculopathy, choroiditis, and retinitis.

Pilot study

A pilot study was done on 10% (7 participants) of the sample size using the same selection criteria. This was to pretest the questionnaire, the screening procedure, data entry, and analysis processes. This was done a month before the actual study. These participants were not included in the main study.

Definition of terms

Keratoconjunctivitis sicca (Dry eye): In this study was defined as dysfunction of the tear film and ocular surface presenting with mild (0-4), moderate (5-7) or severe (>8) symptoms using the SPEED questionnaire or eyes with at least one of abnormal Schirmer test or abnormal TBUT. The SPEED questionnaire was used as a proxy for the measurement of the severity of ocular manifestations in this study [16].

Tear Film Break Up Time (TBUT): Time to the appearance of the first dry spot on the cornea after staining with fluorescein. Diagnosis of dry eye is based on TBUT <10 secs [18].

Schirmer test 1: Extent of wetting of Schirmer strip placed in the lower fornix for 5 minutes. A reading equal to or more than 10 mm wetting in 5 minutes is considered normal while less than 10 mm is considered abnormal, thus indicative of dry eye disease [19].

Normal/Mild visual impairment: Presenting distance vision better or equal to 6/18 (20/40) in the better eye.

Moderate visual impairment: Presenting distance VA of worse than 6/18 (20/70) but better than or equal to 6/60 (20/200) in the better eye.

Severe visual impairment: Presenting distance VA of worse than 6/60 (20/200) better than or equal to 3/60 (20/400) in the better eye.

Blindness: Visual acuity of worse than 3/60 (20/500), Visual fields <10 degrees from fixation.

Data analysis

Data entered in the questionnaire was checked for completeness and accuracy at the end of the screening and eye examination process. All the data was recorded and analyzed using Stata statistics software version 13 (copyright StataCorp LP, USA). Summary statistics to calculate point estimates for all background characteristics and other variables were pre-

sented. Data were reported as frequencies and proportions (%) for categorical variables; and means for continuous variables. Also, the effect of various independent variables (such as age, sex, socioeconomic status, adherence to treatment, and co-morbidities) on the probability of having an association with the ocular manifestation of SLE was assessed. Fisher's exact test was employed to test for differences in proportions between the categorical variables. A logistic regression model was used to estimate determinants of ocular manifestations in SLE. Only variables that show statistical significance found in the univariable analysis were included in the multivariable model. All p values <0.05 were considered statistically significant. For the logistic regression model, age was regrouped around the mean age, the occupation was grouped into a binary variable, and the duration of SLE was regrouped into 3. This was due to the small numbers in the categories of these variables.

Table 1: Socio-demographic and clinical status of the participants.

Variable	Grouping	N 71	(%) (100)
Gender	Male Female	4 67	5.63 94.37
Age grouping	18 to 27 years 28 to 37 years 38 to 47 years 48 to 57 years 58 to 67 years 68 to 77 years	15 22 17 8 6 3	21.13 30.99 23.94 11.27 8.45 4.23
Duration of the Disease	<1 year 1-5 years 6-10 years ≥10	16 42 7 6	22.54 59.15 9.86 8.45
Occupation	Employed Unemployed Retired	47 21 3	66.20 29.58 4.23
Cigarette Smoking	Never smoked Current smoker Past smoker	66 2 3	92.96 2.86 4.23
Hypertensive status	Hypertensive Not Hypertensive	16 55	22.54 77.46
Diabetic status	Diabetic Non-diabetic	5 66	7.04 92.96
Sickle cell disease status	HbSS +ve HbSS -ve	3 68	4.23 95.77
Cumulative hydroxy-chloroquine dosage	<1000g ≥1000g	13 58	18.31 81.69

Results

A total of 71 patients were studied. The age range of the study population was 18 to 74 years with a mean age of 38.7 years and an interquartile range of 48. There were 67 (94.37%) females. Over one-third; 22(30.99%) were within the 28 to 37 years bracket. Most of the participants have had SLE for 1-5 years 42(59.15%), either employed at an organisation or self-employed 47(66.20%), had never smoked a cigarette before 66(92.96%); had no history of hypertension 55(77.46%), no history of diabetes 66(92.96) and no history of sickle cell disease 68(95.77%). Over four-fifths of the participants, 58(81.69%) had a total of ≥1000 g cumulative dose of hydroxyl chloroquine throughout their illness as shown in Table 1.

Taking the medication independently, the proportion of participants on prednisolone was approximately 93%, those on hydroxyl chloroquine was 69%, and 41% on other medications that include azathioprine, methotrexate, and mycophenolate as shown in Table 2.

Table 2: SLE Medications in use during the study.

Medication	N (%)		
	Yes	No	Total
Prednisolone	66(92.96)	5(7.04)	**71(100)**
Hydroxychloroquine	49 (69.01)	22(30.99)	**71(100)**
Other medications *(azathioprine, methotrexate, mycophenolate)*	29(40.85)	42(59.15)	**71(100)**

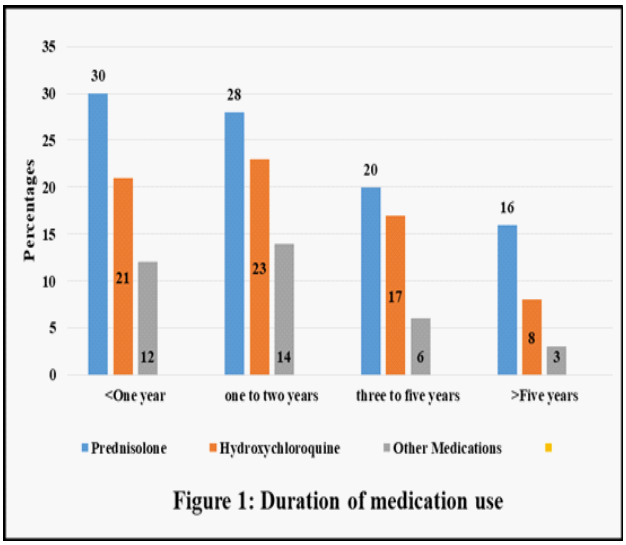

Figure 1: Duration of medication use

Figure 1: Duration of medication use.

Table 3: Ocular history.

Symptom	Responses – N (%)			
	Never	Sometimes	Often	Always
Red eyes	48(68)	20(28)	2(3)	1(1)
Lid rash or eruption	41(58)	23(32)	6(8)	1(1)
Double vision	66(93)	5(7)	0(0)	0(0)
Difficulty looking at light	40(56)	23(32)	4(6)	4(6)
Scattering of lights	67(94)	3(4)	0(0)	1(1)
Eye floaters	61(86)	10(14)	0(0)	0(0)
Flashing lights in eyes	68(96)	3(4)	0(0)	0(0)
Distortion of images	67(94)	4(6)	0(0)	0(0)

The most frequently used medication in the SLE patients was prednisolone as seen in figure 1 followed by hydroxychloroquine and other medications in all the categories of duration of use. The majority of the participants (49%) reported that they had missed their medications on one or more occasions even though a slightly smaller proportion (45%) remained compliant with their medication. There is a small percentage of the participants (6%) that had not been commenced on any medication, these were the most recently diagnosed participants.

The majority of their symptoms were occasional. The most frequent ocular symptom reported by participants was difficulty in looking at the light (31: 44% of participants). The proportion of participants who had red eyes were 23(34%), lid rash or eruptions 30(41%), double vision 5(7%), scattering of light 4(5%), floaters10 (14%), flashing of light 3(4%) and distortion of images was 4(6%) as shown in Table 3.

Visual status

Most of the participants had normal/mild visual impairment 58(81.69%) in the right eye and 57(80.28%) in the left eye. In those with diminished vision, the causes were due to cataract, pale cupped discs, and maculopathy. The intraocular pressure was normal in 69(97.18%) and 70(98.59%) of the right and left eye, respectively. The Amsler's grid was normal in 66(92.96%) and 67(94.37%) of the right and left eyes, respectively as shown in Table 4.

Table 5 shows the common ocular findings stratified by age grouping into 2 categories for ease of comparison. There was one missing value for Schirmer's test, thus this variable was analyzed based on data from 70 participants. There was a significantly higher frequency of cataract in the older age group (48 to 74 years) 47.06% as against the younger age (18 to 47 years) 5.56% with a p-value of < 0.001. However, the frequency of maculopathy was higher in the younger age group (22.22%) than in the older group (5.88%) although this was not significant. The prevalence of dry eye disease was 71.43% using both the TBUT and the Schirmer's test but the prevalence using the individual diagnostic tool was 56.34% and 51.43% for TBUT and Schirmer's test, respectively. Dry eye disease prevalence using the 3 different diagnostic classifications was higher in the older age group as compared with the younger age group but the difference was not statistically significant. Other ocular findings with their frequency of occurrence include lid erythematous rash 1(1.14%), lid oedema 1(1.14%), meibomitis 1(1.14%), Episcleritis 1(1.14%) Pterygium was 3(4.23%), epithelial defect 4(5.63%), relative afferent pupillary defect 1(1.14%), cataract in 10(14.08%), pale cupped disc 3(4.23%) and retinitis 1(1.14%).

Table 4: Ocular examination test findings.

Examination	Grading	Right eye N (%)	Left eye N (%)
Visual acuity	Normal/Mild visual impairment Moderate visual impairment Severe visual impairment	58(81.69) 10(14.08) 3(4.23)	57(80.28) 9(12.68) 5(7.04)
Intraocular pressure	Normal Abnormal	69(97.18) 2(2.82)	70(98.59) 1(1.41)
TBUT	Normal Abnormal	37(52.11) 34(47.89)	38(53.52) 33(46.48)
Schirmer's test	Normal Abnormal	36(50.70) 35(49.30)	39(55.71) 31(44.29)
Amsler's Grid	Normal Abnormal	66(92.96) 5(7.04)	67(94.37) 4(5.63)

Table 5: Ocular examination test findings.

	Age grouping			
Ocular findings	**18 to 47 yrs**	**48 to 74 yrs**	**P-value**	**Total**
Lens				
Normal Cataract Total	51 (94.44) 3 (5.56) 54 (100)	9 (52.94) 8 (47.06) 17 (100)	<0.00	60 (84.51%) 11 (15.49%) 71 (100)
Fundus				
Normal Maculopathy Pale and cupped disc Retinitis Total	40 (74.07) 12 (22.22) 1 (1.85) 1 (1.85) 54 (100)	14 (82.35) 1 (5.88) 2 (11.76) 0 (0) 17 (100)	 0.27 0.19 1.00	54 (76.06%) 13 (18.31%) 3 (4.23%) 1 (1.41%) 71 (100)
Cornea				
TBUT test only Normal Abnormal Total	 27 (50.00) 27 (50.00) 54 (100)	 4 (23.53) 13 (76.47) 17 (100)	 0.09	 31 (43.66) 40 (56.34) 71 (100)
Schirmer's test only Normal Abnormal Total	 28 (52.83) 25 (47.17) 53 (100)	 6 (35.29) 11 (64.71) 17 (64.71)	 0.27	 34 (48.57) 36 (51.43) 70 (100)
TBUT + Schirmer's test Normal Abnormal Total	 17 (32.08) 36 (67.92) 53 (100)	 3 (17.65) 14 (82.35) 17 (100)	 0.36	 20 (28.57) 50 (71.43) 70 (100)

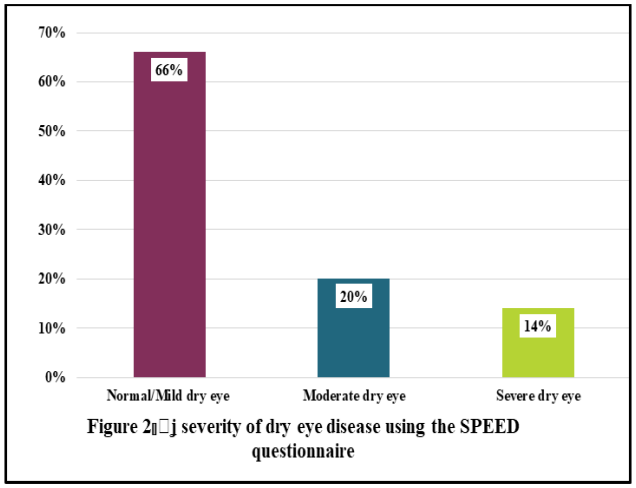

Figure 2: Severity of dry eye disease using the SPEED questionnaire.

Table 6: The cumulative dose of hydroxychloroquine (HCQ) with the frequency of maculopathy.

	Maculopathy	No maculopathy	Total
HCQ >1000g	11 (19%)	47 (81%)	58 (100%)
HCQ <1000g	2 (15%)	11 (85%)	13 (100%)
Total	13 (18%)	58 (82%)	71 (100%)

p=1.00

Figure 2 shows the severity classification of dry eye disease using the SPEED questionnaire. Most of the participants had normal/mild dry eye disease (66%) followed by moderate dry eye (20%) and severe dry eye (14%).

Table 6 shows the relationship between the cumulative doses of HCQ to the proportion of participants that develop maculopathy. Participants with cumulative dose >1000g had a slightly higher proportion of maculopathy 11 out of 58 (19%) as compared to those with a cumulative dose of less than 1000g who were 2 out of 13 (15%). However, this was not statistically significant [p value = 1.00]. Overall, 18% of the study population had one form of maculopathy in either eye irrespective of the cumulative dosage of HCQ.

Analyzing the relationship of the predictor variables shown in Table VII with the presence of cataract in any one of the eyes of the study participants, there was a statistically significant increase in odds of having a cataract with every year of increase in age (OR – 1.15, 95% CI – 1.07 to 1.24, p - <0.001). No other variable showed any statistical significance with the presence of a cataract and thus a multivariate analysis was not performed.

Table 7: The cumulative dose of hydroxychloroquine (HCQ) with the frequency of maculopathy.

Variable	OR	95% CI	P-value
Age	1.15	1.07 to 1.24	<0.001
Chloroquine use No Yes	 1.00 0.75	0.20 to 2.88	0.68
Prednisolone use No Yes	 1.00 0.71	0.07 to 7.07	0.77
Duration of illness <1 year 1 to 5 years ≥ 6 years	 1.00 1.17 2.10	 0.21 to 6.48 0.29 to 14.98	 0.86 0.46
Cumulative HCQ dose ≤1000g >1000g	 1.00 0.53	0.12 to 2.37	0.41

Table 8: Univariate analysis of predictors associated with the presence of Maculopathy.

Variable	OR	95% CI	P-value
Age	0.94	0.89 to 1.00	0.05
Chloroquine use No Yes	 1.00 1.62	0.40 to 6.60	0.50
Prednisolone use No Yes	 1.00 0.89	0.09 to 8.68	0.92
Duration of illness <1 year 1 to 5 years ≥ 6 years	 1.00 1.65 2.10	 0.31 to 8.75 0.29 to 14.98	 0.56 0.46
Cumulative HCQ dose ≤1000g >1000g	 1.00 1.29	0.25 to 6.65	0.76

Table 9: Univariate analysis of predictors associated with the presence of Maculopathy.

Variable	OR	95% CI	P-value
Age	1.07	1.02 to 1.13	0.01*
Chloroquine use No Yes	 1.00 0.44	0.13 to 1.53	0.20
Prednisolone use No Yes	 1.00 0.61	0.06 to 5.77	0.66
Duration of illness <1 year 1 to 5 years ≥ 6 years	 1.00 1.45 3.30	 0.43 to 4.89 0.54 to 20.27	 0.55 0.20
Cumulative HCQ dose ≤1000g >1000g	 1.00 0.71	0.17 to 2.89	0.63

Table 8 describes the univariate analysis showing the relationship of some of the predictor variables with the presence of maculopathy in any of the eyes. Only age showed some very weak statistical significance of a reduction in the likelihood of having maculopathy with increasing age as indicated by an odds ratio of 0.94, 95% CI of 0.89 to 1.00, and p-value of 0.05. Although the other variables showed some increased odds except prednisolone use, these were not statistically significant.

Table 10: Univariate analysis of predictors associated with dry eye disease severity.

Variable	OR	95% CI	P-value
Age	0.98	0.95 to 1.02	0.39
Chloroquine use No Yes	 1.00 1.14	0.39 to 3.33	0.81
Prednisolone use No Yes	 1.00 1.00		
Duration of illness <1 year 1 to 5 years ≥ 6 years	 1.00 2.67 2.71	 0.66 to 10.83 0.50 to 14.54	 0.17 0.25
Cumulative HCQ dose ≤1000g >1000g	 1.00 1.89	0.47 to 7.65	0.37

No multivariate analysis was done because it was only one variable that showed statistical significance.

There is a significant odds of having dry eye disease for every year increase in age as evidenced by an odds ratio of 1.07, 95% CI of 1.02 to 1.13, and p-value of 0.01. Although there were increased odds with an increase in the duration of illness, this did not show any statistical significance. Prednisolone use, chloroquine use, and cumulative HCQ dose showed a decrease in odds without any statistical significance as shown in Table IX. Thus, only univariate analysis was performed.

Table 10 shows the association of the variables with dry eye disease severity. Chloroquine use, duration of illness, and cumulative HCQ dose showed some increased odds but these were not statistically significant. None of the other variables showed any association with dry eye disease severity thus there was no need to perform a multivariate analysis.

Discussion

The quality of life of patients with SLE may be adversely affected because of the long-term morbidity associated with the disease [3]. In this study, those that were most affected were within the productive age group of 18 to 47 years, as was observed in other studies although with slightly different mean ages; and were predominantly females [1-3,7,20-23]. The female predominance may be due to the increased autoimmune response in females as compared to males. The age bracket most affected might have a significant economic impact, directly and indirectly. Directly because this is the age when they are expected to be most productive and indirectly due to the burden on their caregivers. Living with such a devastating disease that can also affect their eyes might further reduce their work productivity.

Almost all (94%) of our study participants were on medication. Another study done in Lagos likewise showed that all the study participants were on medication but this was a retrospective study [7]. Those yet to commence medication in this study were newly diagnosed patients. Most of our study participants were on corticosteroids (either oral or intravenous) therapy (93%) and hydroxychloroquine (69%) which are the mainstay in the pharmacological treatment of SLE [1,22,24,25]. This is similar to the report by Resch et al [26] who had the majority of their patients (96%) on systemic glucocorticosteroid and then (85%) chloroquine therapy. About half of our participants reported to have missed their medication on one or more occa-

sions, this is a very important finding as compliance to medication will help reduce the progression of the disease. Another study reported the commonest reason for non-persistence with HCQ treatment to be poor health literacy (73%) [27]. This is not within the scope of this study and further studies may need to be done to determine the possible reason(s) for a high proportion of patients missing their medication.

The commonest ocular history in this study was difficulty looking at light in 31(44%). Other symptoms include redness, and blurred vision as also reported by Dahlia et al [28]. Most studies reviewed did not report symptoms of SLE in their result. Several of the symptoms from this study may be due to the dryness of the ocular surface which may be worsened by exposure to light.

The common ocular manifestations observed in this study were dry eye disease, Cataract, and Maculopathy. Other negligible ocular findings included lid erythematous rash, lid oedema meibomitis, episcleritis, pterygium, epithelial defect, relative afferent pupillary defect, pale cupped disc, and retinitis.

One out of every six of our study participants had one form of cataract or the other. The frequency of cataract in this study was lower compared to the study reported by Rosanna et al [29] who found corticosteroid-induced cataract in (21.4%) of their study participants. This lower percentage may be because our study had lower numbers of participants in the older age group, given the fact that the risk of cataract strongly increased with age (p-value of <0.001). Prednisolone use, chloroquine use, and cumulative HCQ were neither significantly associated with cataract as might have been expected [14,25] nor the duration of illness. This might be because the participants may have had interrupted prednisolone therapy which was not captured in this study. Further studies to examine this might be required.

Although participants with a cumulative HCQ dose of ≥1000g were likely to develop maculopathy as compared to those with a cumulative dose of less than 1000g, this was not significant. Michaelides et al [30] reported that the risk of maculopathy increases with the dose and duration of HCQ use, this was not found in our study. This is likely due to the lower percentage of our participants having the disease for more than 5 years. It has been documented that the risk of maculopathy increases with long-term administration of HCQ use usually greater than 5 years and a high cumulative dose [25,29,30]. Thus it is expected that maculopathy may increase as the disease progresses in our study participants which may be demonstrated if they are followed up for some time possibly in a prospective cohort study. Therefore, it is important to routinely refer SLE patients for eye screening before they reach the 1000g cumulative dose of HCQ [30]. Age, expectedly was weakly associated with the risk of maculopathy. Ocular manifestations such as lupus choroidopathy, retinal vasculitis [31] central serous choroidopathy, and microangiopathy characterized by cotton wool spots, hard exudates, microaneurysms and retinal hemorrhages as reported in non-whites and Asian population [10,32] were not found in our study. This could be due to the choice of outpatients from the Rheumatology Clinic as these patients are more clinically stable compared to those on the ward.

Dry eye disease was the most prevalent (71%) ocular finding, as indicated by several authors [1,9,10,14,25,29,33,34]. The prevalence of dry eye disease using the Schirmer's test alone was 51% and 56% using TBUT alone. Our overall prevalence rate of dry eye disease was higher than the report of most studies probably because of our definition of dry eye disease using either an abnormal value of Schirmer's test or TBUT compared to a single diagnostic tool used in other studies; as most other studies either used Schirmers test alone or TBUT alone. There is presently no defined combination diagnostic tool specific for dry eye disease and for better comparison to be made, there should be a defined list of diagnostic tools to be used in studies on SLE patients. Using the SPEED questionnaire to assess the severity of the participant's symptoms, a higher proportion (66%) of participants had normal/mild dry eye disease. The SPEED questionnaire has been validated to assess the frequency and severity of dry eye disease [17]. Increasing age was the only significant predictor of dry eye disease. This is not surprising as it is expected that as the patient ages, there will be some age-related deterioration as well as disease-related morbidity changes in the eyes. There was no statistically significant predictor for the severity of dry eye disease in this study. This test of association was not reported in most literature. This means that in this study, there was no risk factor associated with the severity of ocular manifestation as defined by the presence of dry eye disease using the SPEED questionnaire. Probably a much larger sample size might be needed to detect an association, or a case-control study might be useful especially due to the rarity of SLE disease.

Strengths

1. The sample size was larger than most of the comparative studies done to determine the ocular manifestation of systemic lupus erythematosus.

2. The ocular examinations were done solely by the principal investigator which eliminates inter-observer differences that might have biased our findings.

3. This study assessed the possible risk factors for the severity of dry eye disease which was not commonly reported by most of the comparative studies.

Limitations of this study

Optical coherence tomography and multifocal electroretinogram should have been included as screening investigations because of their usefulness in detecting maculopathy before it is visible in the fundus but were not used due to the unavailability of the equipment. The dosage of prednisolone use was not recorded in this study as this might have been used for better comparison with other studies.

Conclusion

SLE may manifest in the different parts of the eye and visual pathway with varying severity and frequency. In this study, Dry Eye Disease was the commonest ocular manifestation with a prevalence of 71%. Cataract and maculopathy were also common in these participants with the risk increasing with age. There is a likely dose-related relationship between hydroxychloroquine and the development of maculopathy. Participants with a cumulative dose of greater than 1000g were more likely to develop maculopathy but this was not statistically significant. There was no statistically significant predictor for the severity of dry eye disease in this study.

Recommendations

Findings from this study have shown that there is a high occurrence of ocular involvement in Systemic lupus erythematosus and dry eye is the commonest sign. There is, therefore,

the need to create awareness amongst Rheumatologists, physicians, and ophthalmologists on the prevalence of dry eye disease in SLE patients and other ocular symptoms and signs to make recommendations that will improve timely diagnosis.

1. It is therefore recommended that the SPEED questionnaire be adapted for use in SLE patients to detect dry eye disease in rheumatology clinics.

2. The primary physician should routinely refer all SLE patients for baseline eye examination and more importantly when the cumulative dosage of HCQ is reaching 1000g, especially in older age groups.

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