Retinal Manifestations in Systemic Lupus Erythematosus: Evaluating the Impact of Visual Impairment and Hydroxychloroquine Toxicity: A cross-sectional study in Saudi Arabia

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ABSTRACT

Systemic lupus erythematosus (SLE) is highly heterogeneous clinically and immunologically, and the precise recognition of the disease's various manifestations may help subdivide patients into subgroups with varying prognostic and therapeutic implications. Therefore, the current study aimed to assess the prevalence and characteristics of retinal manifestations in patients with SLE, with a particular focus on the relationship between visual impairment, retinal drug toxicity (specifically hydroxychloroquine retinopathy), and their implications for clinical management and treatment protocols. This study conducted a retrospective cross-sectional study to assess the prevalence and characteristics of retinal manifestations in patients with SLE. The study spanned 20 years between January 1, 2001, and December 31, 2021, and was conducted in the Internal Medicine department of King Fahad Medical City in Riyadh, Saudi Arabia. In the current study, we collected data from 327 patients diagnosed with SLE. Around 10.8% of patients with SLE had chronic kidney disease in the last three months, evidenced by elevated creatinine serum levels > 110 µmol/l or 1.2 mg/dl. Visual acuity was normal in 99.1% of right eyes and 97.9% of left eyes, with all patients having normal intraocular pressure. The only retinal manifestation identified was hydroxychloroquine retinopathy in 1.2% of patients. No cases of SLE retinopathy or any other drug-related retinal side effects were identified. The majority of patients were prescribed hydroxychloroquine. This research revealed that most SLE patients had normal intraocular pressure and visual acuity, with few instances of hydroxychloroquine retinopathy. Large-scale longitudinal studies are needed to enhance our understanding of the relationship between SLE, medication regimens, and ocular manifestations, along with the effect these factors have on visual outcomes.

Keywords: Prevalence; retina; systemic lupus erythematosus; Saudi Arabia

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complicated autoimmune disease affecting many systems in the body. Usually seen in females of childbearing age, the diagnosis can be made in young children as in elderly patients over 70 years of age. The clinical and immunological features of SLE are very variable, and the identification of the varied aspects of the disease may help classify patients into subsets with different prognoses and treatment consequences.[1] The clinician global assessment and the modified SLE disease activity index M-SLEDAI allow the recognition of three distinct illness patterns. There are three main illness patterns: relapsing-remitting, chronically active, and long quiescent. Patients may present with mixed patterns. In addition, clinicians can identify transitions from one illness pattern to another during follow-up. Sizable groups of patients have consistently reported similar clinical features of SLE at the time of diagnosis and throughout the illness. Although ocular involvement is highly prevalent, it has not received much attention in clinical and research settings even though almost any organ may be involved. [1]

Ocular involvement in SLE may present with a diverse range of severity and could involve multiple entities within the eye and along the visual pathway. Therefore, patients with SLE may present with a broad spectrum of disease severity concerning the involvement of the eye. However, it is still the most common association with keratoconjunctivitis sicca, while the most devastating visual complications occur as part of optic nerve involvement and retinal vaso-occlusion. [2]

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The ocular abnormalities could present as the first sign of the disease and might lead to severe ocular morbidity and vision loss. Identification and urgent management of SLE patients by ophthalmologists and rheumatologists is imperative. Previous studies conducted in Saudi Arabia have not investigated the incidence of ocular manifestations in adult patients with SLE.

SLE is a chronic immune system disorder that may impact multiple organ systems. The etiology of this disease is unknown. The discovery of new therapeutic agents has lowered the incidence and mortality rate of a particular condition to some extent. The ocular manifestations of lupus are significant because they indicate that the disease does not occur only in the eyes. Patients should promptly report ocular symptoms to their physician, as these manifestations may indicate extraocular disease. CNS lupus has been associated with severe retinal artery occlusive disease and lupus optic neuropathy. Lupus choroidopathy, among other ocular manifestations, can occur with systemic vascular disease that affects the entire body. [3] Patients with ocular lupus must be seen and evaluated by a rheumatologist to assess whether any problems can be treated or prevented.

Lupus retinopathy is the most common posterior-segment disease among SLE patients. It occurs in a wide range of patients, ranging from 3% to 29% prevalence. It is more likely to occur in patients with severe or uncontrolled disease for a prolonged period. The pathogenesis of lupus retinopathy involves two aspects. First, patients with SLE are susceptible to developing antiphospholipid syndrome, which results in blood clotting in the retinal blood vessels. Furthermore, the immune complexes deposited in the retinal arteries lead to the inflammation mediators and the development of vasculitis. Immune complexes deposited on the endothelial lining of the blood vessels promote complement activation and inflammation mediators. Similarly, the inflammatory response can reduce blood flow and lack of oxygen to tissues. The aim of this study is to evaluate the frequency and characteristics of retinal symptoms in individuals diagnosed with SLE. The specific focus is on investigating the relationship between visual impairment, retinal drug toxicity (particularly hydroxychloroquine retinopathy), and the resulting consequences for clinical management and treatment approaches.

METHODS

A retrospective cross sectional study was conducted to assess the prevalence and characteristics of retinal manifestations in patients with SLE. The study covered a period of 20 years, from January 1, 2001, to December 31, 2021, and took place in the Internal Medicine Department of King Fahad Medical City, Riyadh, Saudi Arabia.

The inclusion criteria for this study were 1) adult patients aged 18 years and above with a confirmed diagnosis of SLE and 2) patients who had undergone detailed retinal examinations performed by their ophthalmologists, including visual acuity (VA) testing, slit lamp biomicroscopy, fundoscopy, and visual field examination. Patients younger than 18 years old, not diagnosed with SLE, or with comorbidities of medical or ocular diseases of others related to other systemic diseases were excluded from the study.

The collected data included demographic information (gender, age), medical history (associated symptoms, duration from symptom onset, comorbidities), laboratory test results, immunological tests, date of treatment initiation, treatment complications, treatment options, and ophthalmological examination findings.

The collected data were managed and organized using Microsoft Excel, and statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 29. Descriptive statistics were employed to present the data, with categorical variables summarized as frequencies and percentages. Continuous variables were reported as means with standard deviations (SD).

This study received approval from the institutional review board (IRB) at King Fahad Medical City, Riyadh, Saudi Arabia (Reference number: 22-113E). Since the study utilized a chart review approach and did not involve direct patient contact, consent forms were not required. Patient identification information was excluded from the collected data to ensure confidentiality and privacy.

RESULTS

This study included a total of 327 individuals who had been diagnosed with SLE. Among these patients, 83.2% were females. The average age was 39.4 years, with a standard deviation of 12.2. Table 1 represents the medical record data of patients diagnosed with SLE. From the sample population, 10.8% of individuals with SLE had chronic kidney disease (CKD) in the past three months, as indicated by high levels of creatinine serum (>110 µmol/l or 1.2 mg/dl). The remaining 89.2% had normal levels of creatinine. In addition, 24.3% of the individuals had hypertension, 9.0% had diabetes mellitus, and 10.6% had a history of neurostroke. About 9.0% of the patients experienced cardiovascular disease. The prevalence of antibodies was as follows: 39.0% for anti-nuclear antibodies, 9.4% for anti-Sm antibodies, 48.6% for anti-dsDNA, 11.3% for anti-cardiolipin antibody (ACLA), 10.9% for lupus anticoagulant (LA), and 16.0% for APLA beta-2 glycoprotein (B2GP) antibody. In addition, 36.7% of the population had a low complement C3. The population of the complement C4 at a low level was 69.4%.

Table 1. Medical history of the patients

Variable		Frequency	Percentage
Chronic kidney disease (last 3 months and persistent high creatinine serum)	>110 µmol/l or 1.2 mg/dl	35	10.8%
Hypertension		80	24.3%
Diabetes mellitus		29	9.0%
Neurostroke		35	10.6%
Cardiovascular disease		29	9.0%
Anti-nuclear antibody (ANA)		127	39.0%
Anti-Sm antibodies		31	9.4%
Anti-dsDNA		159	48.6%
Anticardiolipin antibody (ACLA)		37	11.3%
Lupus anticoagulant (LA)		36	10.9%
beta-2 glycoprotein (B2GP) antibody		52	16.0%
Low complement C3		120	36.7%
Low complement C4		227	69.4%

Table 2 displays the results of eye examinations conducted on the patients. Regarding visual acuity in the right eye, 324 patients (99.1%) had normal vision, while the remaining patients had varying degrees of visual impairment. Similarly, 320 patients (97.9%) had normal visual acuity in the left eye. The intraocular pressure was within the normal range for all patients. For patients with hydroxychloroquine retinopathy showed bulls eye maculopathy clinically. With Oct showing parafoveal loss of the ellipsoid zone. The rest of the patient had a normal fundus exam. The cases of moderate and severe vision impairment were attributed to hydroxychloroquine retinopathy. The remaining cases of vision impairment were due to refractive errors, such as myopia, hyperopia, or astigmatism.

Table 2. Eye examination profile

	Normal/ Near Normal Vision	Mild Vision Impairment (6/12 - 6/18)	Moderate Vision Impairment (<6/18-6/60)	Severe Vision Impairment (<6/60-3/60)
Right Eye	324 (99.1%)	0	1 (0.3%)	1 (0.27%)
Left Eye	320 (97.9%)	0	4 (1.2%)	2 (6.1%)
Intraocular Pressure	**10-21 mmHg (normal)**	**> 21mmHg**	**21**	**< 10 mmHg**
	327 (100.0%)	0		0

Among the retinal manifestations observed in patients with SLE, the only identified manifestation was hydroxychloroquine retinopathy, observed in 4 patients (1.2%). Furthermore, we did not observe SLE retinopathy in the patients examined or identify any other drug-related side effect in the retina.

Table 3 provides information on the treatment regimen of the patients. Most patients (69.7%) were prescribed a dose of 200mg of hydroxychloroquine, while 30.3% received a dose of 400mg. Corticosteroids/prednisolone were administered to 81 patients (24.8%). Around 31 patients (9.5%) received azathioprine, with methotrexate given to 24 patients (7.3%). Cyclosporine was the least commonly prescribed medication, with only four patients (1.2%) receiving it.

Table 3. The treatment regimen of patients

		Frequency	Percentage
Dose of Hydroxychloroquine	200mg	228	69.7%
	400mg	99	30.3%
Corticosteroids/prednisolone		81	24.8%
Methotrexate		24	7.3%
Azathioprine		31	9.5%
Cyclosporine		4	1.2%

DISCUSSION

This study found that most SLE patients were females, accounting for 83.2% of the sample. This result is consistent with the literature,[3] in which SLE shows a remarkable female predominance of the cases, reaching a nine-fold higher prevalence among females than males. [4] This variation between genders underlines the necessity of considering sex aspects in the diagnosis of SLE. Several factors may result in the difference in SLE incidence between sexes. These include sex-specific environmental exposures, [5] differences in the regulation of genes by sex, [3] genetic differences related to sex chromosomes, [6] intrinsic differences in the immune system between the sexes, and sex hormones such as estrogen. [7] The increased prevalence of SLE in females has been linked to the effect of estrogen hormones. [7] Estrogen modulates immune responses and affects predisposition to autoimmune diseases such as SLE. Nevertheless, SLE is most prevalent in the childbearing year but can appear at any age. [8] Moreover, a prior study [9] also indicates that the gut microbiome contributes to sex differences, such that different gut flora may be responsible for different behaviors of the immune system in males and females.

In this study, about 10.8% of individuals with SLE suffered from CKD. This prevalence is slightly lower than in many other studies, which reported that as many as 40% to 70% of SLE patients develop kidney disease, mostly lupus nephritis, in the course of their disease. SLE significantly contributes to both end-stage renal disease (ESRD) and CKD, and renal involvement occurs in about 3:5 of SLE patients. [10] Of these, 1:10 to 1:5 eventually develops ESRD. [11] Moreover, the development of ESRD and CKD due to lupus nephritis is a principal reason for mortality among SLE patients. [12]

In this study, visual acuity of the right eye was normal in 324 patients (99.1%), with the rest suffering different degrees of visual impairment. Similarly, visual acuity of the left eye was normal in 320 patients (97.9%), while intraocular pressure was normal in all the patients. These findings indicate that the visual status among SLE patients is good, with very few patients experiencing visual impairment, implying good clinical oversight and good management. In SLE patients, regular ophthalmological examinations are essential for the early detection and management of potential visual complications.

A prior study has revealed that the loss of vision might be a potential consequence of SLE, with the most frequent reason for this being retinopathy; 7% of SLE patients suffer from a decrease in visual acuity, thus emphasizing the importance of vision monitoring in these patients. Another prior study demonstrated that 22.6% of SLE patients have reduced visual acuity. [13] On the other hand, the high percentage of patients with normal visuals suggests a better outcome in vision. This disparity may arise due to variations in study populations, disease severity, or differences in management and treatment protocols.

Interestingly, despite fully preserved visual acuity, SLE patients with antiphospholipid syndrome might suffer from extreme visual function loss that needs immediate intervention by ophthalmologists and rheumatologists. [14] This factor suggests that ocular evaluations in SLE patients must be comprehensive, even if visual deficits are absent.

Regarding intraocular pressure, homeostasis is required to ensure the general function and health of the eye.[15] Raised or lowered intraocular pressure can result in destructive outcomes such as choroidal detachment, uveitis, and glaucoma. [15] High intraocular pressure is an important indicator; leaving high intraocular pressure untreated can cause permanent damage to the optic nerve. The finding that all patients had normal intraocular pressure is promising, indicating that this cohort is well monitored and managed.

In this study, the only identified retinal manifestation observed in patients with SLE was hydroxychloroquine retinopathy, which was identified in 4 patients (1.2%). Furthermore, no SLE retinopathy was observed in the patients examined. These findings suggest a relatively low prevalence of retinal complications among SLE patients. Though present in a small subset of patients, hydroxychloroquine retinopathy is the only retinal problem observed. This finding suggests that monitoring hydroxychloroquine use and assuring appropriate dosing would reduce the risk of retinopathy.

Hydroxychloroquine and chloroquine are cornerstones in SLE management; they reduce the risk of complications, delay disease progression, maintain remission, and reduce the frequency of disease flares (especially lupus nephritis). The prevalence of hydroxychloroquine-induced retinopathy was variable in different studies, with rates ranging between 0.3% and 13.8%. [4] It was 1.2% in this study population, which may reflect successful dosing, adequate monitoring, and early intervention practices for the participants. In addition, the low prevalence of hydroxychloroquine retinopathy may be because all SLE patients could use hydroxychloroquine without risk (low-risk profile for the medication) irrespective of their activity of SLE, gender, or age, as concluded by a prior study. [16] This finding could be due to patients' adherence to guidelines for dosage, duration of use, and regular ophthalmologic screening.

Several risk factors are recognized for hydroxychloroquine retinopathy, including concomitant tamoxifen use, deficient renal function, prolonged exposure [equal or above five years], [17] and high daily doses [more than 5 mg/kg/day]. [17] More recently, patients with high myopia

and lower body weight are at significantly higher risk of developing hydroxychloroquine retinopathy. [12] The relatively low incidence in this study may reflect the careful consideration of these risk factors in clinical practice for the participants and emphasize the importance of individualized treatment with attentive monitoring.

Retinopathy is irreversible and currently has no effective treatment. [17] Thus, early recognition and preventive strategies are vital to avoid central visual loss. [17] The finding of this study that there is no SLE-related retinopathy suggests that the early detection and management strategies for retinal health may be very effective for the cohort of this study. According to the American Academy of Ophthalmology recommendations, baseline ophthalmologic examinations within the first year of initiating long-term hydroxychloroquine or chloroquine therapy must document any pre-existing ocular conditions and establish a record of the functional status and fundus appearance. [17] Subsequently, annual screening is recommended, particularly after five years of exposure, unless there are known significant risk factors that require earlier evaluations. [17]

Furthermore, the absence of any drug-related side effects in the retina underlines the efficacy of current patient management protocols. These protocols may include appropriate dosing, regular monitoring, and inter-professional collaboration, which contribute to maintaining optimal ocular health for SLE patients. This observation is important since almost all the medications used for SLE have been reported to cause adverse effects on different parts of the eye.

Hydroxychloroquine has been an essential treatment for SLE. In Europe, about 67.7% of SLE patients presently use hydroxychloroquine, indicating the usual dosage in treatment. [18] In this study, most patients (69.7%) were prescribed a dose of 200mg of hydroxychloroquine, while 30.3% received a dose of 400mg; dosages fall into the recommended dosages. [19] For patients whose weight exceeds 80 kg, 400 mg is the recommended maximum dose. [20] According to the 2016 guidelines of the American Academy of Ophthalmology, the safe daily dose of hydroxychloroquine should not exceed 5 mg/kg of body weight to reduce the risk of retinopathy. The dosing patterns adhere to these safe limits since most patients were prescribed doses within this range. [17]

Corticosteroids also remain influential in SLE management because of their potent anti-inflammatory effects. [21] Their use is associated with significant side effects, including cataracts, coronary artery disease, and osteoporotic fractures. Of the patients in this study, 24.8% received treatment with corticosteroids/prednisolone without any adverse effects reported, which reflects a careful balance between benefits and risks concerning steroid therapy. High doses of prednisone, particularly above 50 mg/day, result in saturation of the glucocorticoid receptors with minimal additional anti-inflammatory effects but with increased adverse outcomes. The use of pulse doses of intravenous prednisolone has been effective in rapid remission and avoids the need for high oral doses over a long time. [22]

Immunosuppressive treatment with azathioprine plays a crucial role in SLE management, most significantly in the remission-induction and control of moderate to severe lupus. In this study, 9.5% of the patients were on azathioprine, and 7.3% were on methotrexate. Methotrexate is efficacious in handling mucocutaneous and musculoskeletal manifestations of SLE [1]. Cyclosporine, a calcineurin inhibitor, was given to a small proportion of our studied patients (1.2%), reflecting its role in specialized cases such as lupus nephritis, [1] where it could be added to standard induction therapy to enhance remission rates.

Finally, the results regarding the SLE treatment approach align with guidelines and practice. Predominant use of hydroxychloroquine and reasonable use of corticosteroids and immunosuppressive medications emphasize balancing efficacy with safety. Thus, adhering to SLE guidelines and attentiveness in monitoring is recommended, which will aid effective management of SLE with minimum adverse effects risk.

This study has limitations. The use of cross-sectional study design restricted the ability to examine causality among the study variables. As a single-center study, this might have affected the generalizability of the study findings.

CONCLUSION

This study found that SLE patients mostly had normal visual acuity and intraocular pressure, with limited cases of hydroxychloroquine retinopathy. No cases of SLE retinopathy or any other drug-related retinal complication were found in the patients under study. Hydroxychloroquine was the most commonly prescribed medication for the patients. Further research in this area must comprise large-scale longitudinal studies that aim to understand better the relationship between SLE, medication regimens, and ocular manifestations and their impact on visual outcomes.

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REFERENCES

1. Fanouriakis A, Tziolos N, Bertsias G, et al. Update on the diagnosis and management of systemic lupus erythematosus. Ann rheum dise 2021;80(1):14-25.
2. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann rheum dise 2024;83(1):15-29.
3. Yao C, Joehanes R, Johnson AD, et al. Sex- and age-interacting eQTLs in human complex diseases. Hum Mol Genet 2014;23(7):1947-1956.
4. Abdelbaky MSE, El Mamoun TA, Mabrouk FI, et al. Frequency and risk factors for hydroxychloroquine retinopathy among patients with systemic lupus erythematosus. Egypt J Intern Med 2021;33(1):1-18.
5. Parks CG, De Roos AJ. Pesticides, chemical and industrial exposures in relation to systemic lupus erythematosus. Lupus 2014;23(6):527-536.
6. Liu K, Kurien BT, Zimmerman SL, et al. X Chromosome Dose and Sex Bias in Autoimmune Diseases: Increased Prevalence of 47,XXX in Systemic Lupus Erythematosus and Sjögren's Syndrome. Arthritis Rheumatol 2016;68(5):1290-1300.
7. Chang R, Xiang S, Jin Y, et al. Hormone and reproductive factors and risk of systemic lupus erythematosus: a Mendelian randomized study. Immunologic research 2024; 1(1): 1-11.
8. Pan L, Lu MP, Wang JH, et al. Immunological pathogenesis and treatment of systemic lupus erythematosus. World jour pedia 2020;16(1):19-30.

9. Gomez A, Luckey D, Taneja V. The gut microbiome in autoimmunity: Sex matters. Clin Immunol 2015;159(2):154-162.
10. Parodis I, Tamirou F, Houssiau FA. Prediction of prognosis and renal outcome in lupus nephritis. Lupus Sci Med 2020;7(1):1-13
11. Maroz N, Segal MS. Lupus nephritis and end-stage kidney disease. Am J Med Sci 2013;346(4):319-323.
12. Kao JH, Lai TT, Lu CH, et al. Characteristics and Potential Risk Factors of Hydroxychloroquine Retinopathy in Patients with Systemic Lupus Erythematosus: Focusing on Asian Population. J Ocul Pharmacol Ther 2022;38(10):728-733.
13. Turk MA, Hayworth JL, Nevskaya T, et al. Ocular Manifestations in Rheumatoid Arthritis, Connective Tissue Disease, and Vasculitis: A Systematic Review and Metaanalysis. J Rheumatol 2021;48(1):25-34.
14. Dmuchowska DA, Grochowski ET, Goździkiewicz-Łapińska J, et al. Full visual acuity may be misleading in accompanying antiphospholipid syndrome: a case of bilateral fovea-sparing retinopathy in a patient with systemic lupus erythematosus. Pol Arch Intern Med 2020;130(10):887-890.
15. Machiele R, Motlagh M, Patel BC. Intraocular pressure. Cureus 2018; 1(1): 1-12.
16. Eo DR, Lee MG, Ham DI, et al. Frequency and Clinical Characteristics of Hydroxychloroquine Retinopathy in Korean Patients with Rheumatologic Diseases. J Korean Med Sci 2017;32(3):522-527.
17. Marmor MF, Kellner U, Lai TY, et al. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology 2016;123(6):1386-1394.
18. Osmani Z, Schrama TJ, Zacouris-Verweij W, et al. Hydroxychloroquine treatment in European patients with lupus erythematosus: dosing, retinopathy screening and adherence. Lupus Sci Med 2021;8(1): 1-15.
19. Wallace DJ, Tse K, Hanrahan L, et al. Hydroxychloroquine usage in US patients, their experiences of tolerability and adherence, and implications for treatment: survey results from 3127 patients with SLE conducted by the Lupus Foundation of America. Lupus Sci Med 2019;6(1): 1-13.
20. Dima A, Jurcut C, Chasset F, et al. Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge. Ther Adv Musculoskelet Dis 2022;14(1): 1-17.
21. Thamer M, Hernán MA, Zhang Y, Cotter D, Petri M. Prednisone, lupus activity, and permanent organ damage. J Rheumatol 2009;36(3):560-564.
22. Ruiz-Irastorza G, Ruiz-Estevez B, Lazaro E, et al. Prolonged remission in SLE is possible by using reduced doses of prednisone: An observational study from the Lupus-Cruces and Lupus-Bordeaux inception cohorts. Autoimmun Rev 2019;18(9): 1-10.