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Chloroquine, Hydroxychloroquine and Hearing Loss: A Study in Systemic Lupus Erythematosus Patients

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Objectives/Hypothesis: Antimalarial drugs (chloroquine and hydroxychloroquine) are widely used for the treatment of systemic lupus erythematosus (SLE). However, these drugs may have side effects such as hearing loss. This study aimed to describe the hearing function in SLE patients using antimalarials. Secondarily, this study aimed to investigate whether SLE causes hearing loss and if there are any serological or clinical aspects of this diseases associated with inner ear damage.

Study Design: Cross-sectional study.

Methods: This study included 84 individuals (43 SLE patients and 41 controls) with audiometry and tympanometry tests. Epidemiological, clinical, serological, and treatment profiles of SLE patients were extracted from the charts.

Results: SLE patients had more sensorineural hearing loss than controls (23.2% vs. 0; P = .001). Pure-tone averages in SLE patients using antimalarials and not using antimalarials were similar (8.75 vs. 8.75; P = .63). At 8,000 Hz, antimalarial dug nonusers performed worse than users (10.00 vs. 22.50; P = .03). Tympanometry was normal in all participants. SLE serological and clinical profiles in patients with and without hearing loss were the same (all P = nonsignificant).

Conclusions: There is a high prevalence of hearing loss in SLE that is not affected by antimalarial drug use.

Key Words: Chloroquine, hearing loss, systemic lupus erythematosus, inner ear, antimalarials.

Level of Evidence: 3b

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INTRODUCTION

Chloroquine is a 4-aminoquinoline known since 1934 and considered to be an effective treatment for malaria; hydroxychloroquine is a hydroxylated analog of chloroquine.[1] Nowadays, these two drugs are widely used for the treatment of autoimmune conditions, mainly systemic lupus erythematosus (SLE), and more recently they have been used in COVID-19 treatment.[2,3] They inhibit interferon-α production, which plays a crucial role in SLE pathogenesis by blocking the toll-like receptor 7 and 9 in plasmacytoid dendritic cells.[4] They also have nonimmune positive effects that are important to prevent vascular damage such as antiplatelet aggregation action and improvement of lipid and glycemic profile.[4,5] These drugs reduce the lupus accrual damage and may have a protective effect in patients' survival.[4] Unless there is a contraindication, all lupus patients should be using antimalarials.

However, antimalarials do have side effects; the most known and feared is retinopathy, which causes irreversible loss of vision, but audiovestibular toxicity has also been reported.[6,7]

The study of the effects of antimalarials on hearing loss is difficult, because the underlying autoimmune condition may cause inner ear damage by itself,[8,9] making it difficult to know which one is responsible for the ear damage.

Herein, we studied a sample of SLE patients to determine the role of antimalarial drug use in hearing function. Secondarily, we studied whether SLE causes hearing loss and if there are any serological or clinical aspects of this disease that are associated with the inner ear damage.

MATERIALS AND METHODS

This is a cross-sectional observational study approved by the local Committee of Ethics in Research under the number 61216516.8.0000.0103 and performed in accordance with the Helsinki Declaration. All participants signed consent. To be included, patients had to fulfill at least four of 1997 American College of Rheumatology (ACR) classification criteria for SLE[10] and have had the disease for more than 16 years.

Epidemiological (age, gender, disease duration, and tobacco use), clinical (malar rash, photosensitivity, oral ulcers, discoid lesions, serositis, glomerulonephritis, convulsions, psychosis, hemolytic anemia, leukopenia, lymphocytopenia, and arthritis

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according to the definition of 1997 ACR classification criteria for SLE[10] and considered in a cumulative way) and serological data (anti-dsDNA, anti-Ro/SS-A, anti-La/SS-B, anti-RNP, anti-Sm, anticardiolipin [aCl] IgG, aCl IgM, or lupus anticoagulant and direct Coombs] were extracted from the charts. Presence of antiphospholipid antibody syndrome was diagnosed according to the Sidney criteria.[11]

We included a convenience sample of 43 SLE patients (86 ears) that represent the number of patients who came for regular consultation in a single rheumatology clinic for a period of 6 months and who agreed to participate in the study. As controls, 41 patients' companions (82 ears) paired for age (P = .27) and gender (P = .10) were recruited. The control group lived in the same geographical area and was from the same socioeconomic class as the lupus patients. We excluded from the sample patients presenting with a previous otologic disease (e.g., chronic otitis, otosclerosis, noise-induced hearing loss)

All participants underwent an otolaryngologic evaluation. All individuals agreed to an audiologic assessment that consisted of pure-tone audiometry (at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz), word recognition score (WRS), and tympanometry. Pure-tone average (PTA) using air-conduction thresholds were also calculated. The tests were performed by one examiner, blind to clinical data using a DA 64 model audiometer and TYMP 83 tympanometer (DANPLEX, Taastrup, Denmark). Hearing loss was defined when >25 dB at PTA or isolated frequency.

We collected the data in frequency and contingency tables. The Shapiro-Wilk test was used to judge data distribution, and central tendency was expressed in mean ± standard deviation or median and interquartile range (IQR), respectively, to parametric or nonparametric data distribution.

Comparisons of disease duration, PTA, hearing threshold at each frequency, and WRS in SLE patients using and not using antimalarials, as well as between SLE patients and controls, were done by Mann-Whitney test. Age between SLE patients with and without hearing loss was compared by unpaired t test. Comparisons of clinical and serological profiles in SLE patients with and without hearing loss were done by χ^2 and Fisher tests. The Spearman test was used for the correlation study of PTA with disease duration. The significance adopted was of 5%.

RESULTS

The descriptions of the SLE study sample are in Table I.

In this sample, 37/43 (86.0%) participants used antimalarials for the median period of 7 years (IQR = 2.0–11.2 years); 16/37 or 43.2% used chloroquine and 21/ 37or 56.7% used hydroxychloroquine.

The comparison of audiometric studies in SLE patients using and not using antimalarials is shown in Table II. In the group of antimalarial drug users, 7/37 (18.9%) had sensorineural hearing loss, and in the group of non-users 3/6 (50%) had sensorineural hearing loss (P = .12). Table III shows the comparison of audiometric studies in SLE patients compared to controls. Tympanometry was normal (type A) in all participants. No conductive hearing loss was seen. The comparison of clinical and serological features in SLE patients with and without sensorineural loss is shown in Table IV.

The results of correlation studies of the PTA values with disease duration showed $\rho = -0.04$ (95% confidence interval [CI]: −0.26 to 0.17, P = .68). In 10/43 (23.2%) of

TABLE I.
Main Characteristics of the Systemic Lupus Erythematosus Sample Studied (N = 43).

Female gender	42/43 (97.6%)
Exposed to tobacco (current and previous smokers)	16/42 (38.0%)
Mean age ± SD, yr	40.8 ± 13.0
Mean disease duration ± SD, yr	10.0 ± 6.0
Photosensitivity	29/42 (69.0%)
Discoid lesion	9/42 (21.4%)
Oral ulcers	19/41 (46.3%)
Malar rash	21/43 (48.8%)
Arthritis	30/43 (69.7%)
Serositis	9/42 (21.4%)
Glomerulonephritis	15/43 (34.8%)
Psychosis	2/43 (4.6%)
Convulsions	2/43 (4.6%)
Hemolysis	7/43 (16.2%)
Leukopenia	14/41 (34.1%)
Lymphopenia	7/40 (17.5%)
Thrombocytopenia	10/42 (23.8%)
Secondary antiphospholipid antibody syndrome	6/42 (14.2%)
Anti-dsDNA	16/43 (37.2%)
Anti-Ro/SS-A	20/42 (47.6%)
Anti-La/SS-B	12/43 (27.9%)
Anti-Sm	8/41 (19.5%)
Anti-RNP	9/42 (21.4%)
Anticardiolipin IgG	11/43 (25.5%)
Anticardiolipin IgM	10/43 (23.2%)
Lupus anticoagulant	5/42 (11.9%)
Direct Coombs	5/42 (11.9%)

SD = standard deviation.

TABLE II.
Comparison of Clinical Data, PTA, Hearing Threshold at Each Frequency, and WRS in SLE Patients Using and Not Using Antimalarials.

	With Antimalarials, 74 Ears (IRQ)	Without Antimalarials, 12 Ears (IRQ)	P
Mean age ± SD, yr	46.4 ± 12.7	40.9 ± 13.9	.22
Median SLE duration, yr	8.50 (5.00–14.25)	12.00 (8.25–21.25)	.19
PTA	8.75 (5.00–13.75)	8.75 (5.31–13.44)	.63
250 Hz	10.00 (5.00–18.75)	10.00 (5.00–15.00)	.81
500 Hz	10.00 (5.00–10.00)	7.50 (5.00–15.00)	.63
1,000 Hz	5.00 (0–10.00)	2.50 (0–10.00)	.47
2,000 Hz	5.00 (3.75–15.00)	10.00 (0–15,0)	.64
3,000 Hz	10.00 (5.00–15.00)	12.50 (5.00–18.75)	.43
4,000 Hz	10.00 (5.00–20.00)	15.00 (7.50–20.00)	.39
6,000 Hz	12.50 (5.00–21.25)	20.00 (15.00–25.00)	.07
8,000 Hz	10.00 (8.75–25.00)	22.50 (16.25–33.75)	.03
WRS, %	96.00 (96.00–100.00)	96.00 (96.00–100.00)	.50

IQR = interquartile range; SD = standard deviation; SLE = systemic lupus erythematosus; PTA = pure-tone average; WRS = word recognition score.

the SLE sample patients and in none of the controls, sensorineural loss was detected (odds ratio: 26.0; 95% CI: = 1.4 to 460.7, $P = .001$).

TABLE III.
Comparison of PTA, Hearing Threshold at Each Frequency, and WRS Between SLE Patients and Controls.

	SLE Patients, 86 Ears (IQR)	Controls, 82 Ears (IQR)	*P*
PTA	8.75 (5.00–13.75)	10.00 (5.93–12.50)	.54
250 Hz	10.00 (5.00–15.00)	15.00 (10.00–20.00)	<.0001
500 Hz	10.00 (5.00–10.00)	12.50 (5.00–20.00)	<.0001
1,000 Hz	5.00 (0–10.00)	5.00 (5.00–15.00)	.03
2,000 Hz	5.00 (0–15.00)	10.00 (5.00–15.00)	.65
3,000 Hz	10.00 (5.00–15.00)	10.00 (5.00–15.00)	.40
4,000 Hz	15.00 (5.00–20.00)	10.00 (5.00–15.00)	.002
6,000 Hz	15.00 (8.75–25.00)	15.00 (10.00–25.00)	.37
8,000 Hz	15.00 (10.00–30.00)	10.00 (8.75–15.00)	.09
WRS, %	96.0 (96.0–100.0)	100.0 (100.0–100.0)	<.0001

IQR = interquartile range; SLE = systemic lupus erythematosus; PTA = pure-tone average; WRS = word recognition score.

TABLE IV.
Comparison of Clinical and Serological Features of Systemic Lupus Erythematosus Patients With and Without Sensorineural Hearing Loss.

	With Sensorineural Loss, N = 10	Without Sensorineural Loss, N = 33	*P*
Photosensitivity	6/10 (60%)	23/32 (71.8%)	.69
Discoid lesion	1/10 (10%)	8/32 (25%)	.41
Oral ulcers	4/10 (40%)	15/32 (46.8%)	1.00
Malar rash	3/10 (30%)	18/33 (54.4%)	.28
Arthritis	6/10 (60%)	25/33 (75.5%)	.42
Serositis	3/10 (30%)	6/32 (18.7%)	.66
Glomerulonephritis	5/10 (50%)	10/33 (30.3%)	.28
Psychosis	0	2/33 (6.0%)	1.00
Convulsions	0	2/33 (6.0%)	1.00
Hemolysis	2/10 (20%)	5/33 (15.1%)	.65
Leukopenia	1/10 (10%)	13/32 (40.6%)	.12
Lymphopenia	2/10 (20%)	5/32 (15.6%)	1.00
Thrombocytopenia	2/10 (20%)	8/33 (24.2%)	1.00
Secondary AAF	1/10 (10%)	5/32 (15.6%)	1.00
Anti-dsDNA	3/10 (30%)	13/33 (39.3%)	.71
Anti-Ro/SS-A	5/10 (50%)	15/33 (45.4%)	1.00
Anti-La/SS-B	3/10 (30%)	9/33 (27.2%)	1.00
Anti-Sm	2/10 (20%)	6/31 (19.3%)	1.00
Anti-RNP	2/10 (20%)	7/32 (21.8%)	1.00
Anticardiolipin IgG	2/10 (20%)	9/33 (27.2%)	1.00
Anticardiolipin IgM	2/10 (20%)	8/33 (24.2%)	1.00
Lupus anticoagulant	1/10 (10%)	4/32 (12.5%)	1.00
Direct Coombs	1/10 (10%)	4/32 (12.5%)	1.00

*odds ratio: 18.0, 95% confidence interval: 2.0-160.8.
AAF = - antiphospholipid antibody syndrome.

DISCUSSION

Our results have shown that antimalarial drug use did not associate with hearing loss. A French Pharmacovigilance register study[6] noted that hearing symptoms may occur within 24 hours after the drug initiation, but most of them are present after more than 1 month of antimalarial drug use and are usually reversible. Nevertheless, irreversible functional sequelae can occur.[6,7] We could not prove that patients using antimalarials had more hearing loss than those without them. Instead, at 6,000 Hz a tendency toward and at 8,000 Hz a statistically proven worse performance in nonusers versus users was found. The previously mentioned positive actions of this drug in vascular function[5] could be considered as a possible explanation for this finding. Another work[12] including 30 lupus patients also failed to show that antimalarial drugs are associated with hearing loss as we did. Nowadays, careful attention to daily doses of this medication may be responsible for the decrease in these medications' side effects.

However, in the present study, SLE patients had more sensorineural loss than controls, corroborating the idea that this disease also affects the inner ear. No conductive hearing loss was detected in the present study. Small case series had related a prevalence of 21% to 70% of sensorineural hearing loss associated with this connective tissue disease; conductive hearing loss, in this context, has been associated with the occurrence of associated infections.[8,13,14] Our results are very similar to those of Kastanioudakis et al.[13] that found 21.5% sensorineural hearing loss while studying 43 patients with SLE from Greece.

The present study also shows that it is not possible to recognize the patients with hearing loss by the clinical or serological lupus profile. Gad and Abdulateef[8] described the association between antiphospholipid antibody syndrome and hearing loss in children with SLE. In addition, several case descriptions associate sudden sensorineural hearing loss in SLE with the presence of this group of autoantibodies.[15,16] We could not find associations with either the presence of antiphospholipid antibodies or with the antiphospholipid antibody syndrome, similar to the findings of Roverano et al.[12]

Early detection of hearing loss is important, as the autoimmune etiology may respond to glucocorticoid and immunosuppressive treatment.[17] Because this involvement may progress slowly, and no lupus characteristics are linked to their presence, the clinician attending these patients should perform an active search to establish early treatment and avoid further damage.

Limitations of this study are the low number of included individuals and its cross-sectional design. Our sample of nonusers of antimalarials was small, and data on disease activity and nonsteroidal anti-inflammatory drug use could also have been informative.

CONCLUSION

Our study showed that antimalarials are safe from the auditory point of view, and highlighted the high prevalence of hearing loss in SLE and the fact that no clinical

or serological finding of the disease could help in its detection.

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