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

Jose F. Polanski, PhD; Eloise A. Tanaka, MD; Harymy Barros, MD; Adriana G. Chuchene, AuD; Patricia T. G. Miguel, AuD; Thelma L. Skare, PhD

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. 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. 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. 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. These drugs reduce the lupus accrual damage and may have a protective effect in patients’ survival. 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.

The study of the effects of antimalarials on hearing loss is difficult, because the underlying autoimmune condition may cause inner ear damage by itself, 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. Secondly, 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 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...
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 21/37 or 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.

The results of correlation studies of the PTA values with disease duration showed ρ = −0.04 (95% confidence interval [CI]: −0.26 to 0.17, P = .68). In 10/43 (23.2%) of SLE patients presenting with a previous otologic disease (e.g., chronic otitis, otosclerosis, noise-induced hearing loss) 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 the results of correlation studies of the PTA values with disease duration showed significance adopted was of 5%.

### 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%) |
| Thrombocytopения | 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.

| Frequency, kHz | With Antimalarials, 74 Ears (IRQ) | Without Antimalarials, 12 Ears (IRQ) | P |
|---------------|-----------------------------------|-------------------------------------|---|
| 150           | 46.4 ± 12.7                       | 40.9 ± 13.9                         | .22 |
| 250           | 8.50 (5.00–14.25)                 | 12.00 (8.25–21.25)                 | .19 |
| 500           | 10.00 (5.00–18.75)                | 7.50 (5.00–15.00)                  | .63 |
| 1,000         | 5.00 (0–10.00)                    | 2.50 (0–10.00)                     | .47 |
| 2,000         | 5.00 (3.75–15.00)                 | 10.00 (0–15.00)                    | .64 |
| 3,000         | 10.00 (5.00–15.00)                | 12.50 (5.00–18.75)                 | .43 |
| 4,000         | 10.00 (5.00–20.00)                | 15.00 (7.50–20.00)                 | .39 |
| 6,000         | 12.50 (5.00–21.25)                | 20.00 (15.00–25.00)                | .07 |
| 8,000         | 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.

| Frequency       | 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          | 15.00 (8.75–12.00)           | 15.00 (10.00–15.00)      | <.0001 |
| 1,000 Hz        | 20.00 (10.00–25.00)          | 15.00 (10.00–25.00)      | .37    |
| 2,000 Hz        | 30.00 (10.00–30.00)          | 10.00 (6.75–15.00)       | .09    |
| 8,000 Hz        | 12.50 (5.00–15.00)           | 100.0 (100.0–100.0)      | <.0001 |
| WRS, %          | 96.00 (96.0–100.0)           | 100.0 (100.0–100.0)      |        |

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.

| Autoantibody          | 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 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\(^6\) 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

Polanski et al.: Chloroquine and Hearing Loss in Lupus

Laryngoscope 131: March 2021
or serological finding of the disease could help in its detection.

BIBLIOGRAPHY

1. Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxy analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents* 2007;30:297–308.

2. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol* 2020;16:155–166.

3. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [published online March 20, 2020]. *Int J Antimicrob Agents*. https://doi.org/10.1016/j.ijantimicag.2020.105949

4. Costedoat-Chalumeau N, Dunoguë B, Morel N, Le Guern V, Guettrot-Imbert G. Hydroxychloroquine: a multifaceted treatment in lupus. *Presse Med* 2014;43(pt 2):e167–e180.

5. Flora A, Piga M, Mangoni AA, Bortoluzzi A, Erre GL, Cauli A. Protective effects of hydroxychloroquine against accelerated atherosclerosis in systemic lupus erythematosus. *Mediators Inflamm* 2018;3424136 eCollection 2018. http://dx.doi.org/10.1155/2018/3424136.

6. Jourde-Chiche N, Mancini J, Dagher N, et al. Antimalarial ototoxicity: an underdiagnosed complication? A study of spontaneous reports to the French Pharmacovigilance network. *Ann Rheum Dis* 2012;71:1586.

7. Fernandes MR, Soares DB, Thien CI, Carneiro S. Hydroxychloroquine ototoxicity in a patient with systemic lupus erythematosus. *An Bras Dermatol* 2018;93:469–470.

8. Gad G, Abdulateef H. Function of the audiovestibular system in children with systemic lupus erythematosus. *Carr Allergy Asthma Rep* 2014;14:446.

9. Di Stadio A, Ralli M. Systemic lupus erythematosus and hearing disorders: literature review and meta-analysis of clinical and temporal bone findings. *J Int Med Res* 2017;45:1470–1480.

10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.

11. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.

12. Roverano S, Cassano G, Paira S, et al. Asymptomatic sensorineural hearing loss in patients with systemic lupus erythematosus. *J Clin Rheumatol* 2006;12:217–220.

13. Kastanioudakis I, Ziavra N, Voulgari PV, Exarchakos G, Skervas A, Drosos AA. Ear involvement in systemic lupus erythematosus patients: a comparative study. *J Laryngol Otol* 2002;116:103–107.

14. Karatas E, Onat AM, Durucu C, et al. Audiovestibular disturbance in patients with systemic lupus erythematosus. *Otolaryngol Head Neck Surg* 2007;136:82–86.

15. Compadretti GC, Brandolini C, Tasca I. Sudden sensorineural hearing loss in lupus erythematosus associated with antiphospholipid syndrome: case report and review. *Ann Otol Rhinol Laryngol* 2005;114:214–218.

16. Green L, Miller EB. Sudden sensorineural hearing loss as a first manifestation of systemic lupus erythematosus: association with anticardiolipin antibodies. *Clin Rheumatol* 2001;20:220–222.

17. Khalidi NA, Rebello R, Robertson DD. Sensorineural hearing loss in systemic lupus erythematosus: case report and literature review. *J Laryngol Otol* 2006;122:1371–1376.