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Ear involvement in systemic lupus erythematosus patients: a comparative study

Ioannis Kastanioudakis, M.D., Nausica Ziavra, M.D., Paraskevi V. Voulgari, M.D.*,
Georgios Exarchakos, M.D., Antonios Skevas, M.D., Alexandros A. Drosos, M.D., F.A.C.R.*

Abstract

Ear damage in systemic lupus erythematosus (SLE) patients has been occasionally reported but the frequency and the mechanisms of ear involvement are not well documented. In an attempt to investigate the presence of hearing loss and the possible causes for it we prospectively evaluated 43 SLE patients. All patients underwent a complete ear-nose-throat physical examination and audiological evaluation with pure tone, impedance and speech audiometry. In addition, systemic manifestations of the disease and drug therapy were recorded. Finally, all patients were tested for the presence of autoantibodies. The results were compared with those of 50 age-matched healthy subjects.

Hearing loss (HL) was found in nine patients (22.5 per cent). More specifically, eight patients presented sensorineural hearing loss (SNHL) (21.5 per cent) and only one had conductive hearing loss (CHL) (2.63 per cent). From the patients with SNHL, one had bilateral symmetrical damage, four had bilateral but no symmetrical damage and three patients showed unilateral SNHL. Finally, the patient with CHL had unilateral involvement. There were no statistically significant differences between patients with HL and those without regarding age, disease duration, clinical disease manifestations, autoantibody profile and drug therapy.

In conclusion, one fourth of our SLE patients presented HL, expressed as SNHL affecting mainly the middle and high frequencies, while only one patient had CHL. This is a lower percentage of ear involvement in SLE than that reported by other investigators. The mechanism of ear damage remains unknown. Thus, additional prospective studies are needed to elucidate its pathogenesis.

Key words: Lupus Erythematosis, Systemic; Hearing Loss, Sensorineural; Hearing Loss, Conductive; Pathology

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder of unknown aetiology with prominent clinical and laboratory features and a variable course and prognosis. The hallmark of the immunological aberration is the excessive autoantibody production, some of which may cause cytotoxic damage, while others participate in immune complex (IC) formation resulting in immune inflammation.[1–3] Clinical manifestations include skin and mucous membrane involvement, joint, serous membrane, kidney, lung, brain and heart involvement.[4,5] Ear damage in SLE patients has been occasionally reported.[6–9] However, the frequency and the mechanisms of ear involvement are not well documented. For this reason we investigated ear involvement in SLE patients and discuss the possible pathophysiological mechanisms involved in it.

Patients and methods

Forty-three unselected, consecutive female patients, who fulfilled the American College of Rheumatology (ACR) criteria for SLE,[10] and who were followed up in the out-patient rheumatology clinic were evaluated for hearing loss.

The patients entered in the study had a complete physical and laboratory evaluation. All the systemic manifestations, as well as the current treatment were recorded. In addition, all patients had an immunological evaluation including: rheumatoid factor (RF) (latex text), antinuclear antibodies (ANA) (indirect immunofluorescence), antibodies to Ro(SSA), La(SSB), U_1RNP and Sm using immunodiffusion, anticardiolipin antibodies (aCL) (Elisa) and C_3 and C_4 complement levels. Furthermore lupus anticoagulant was also detected (Kaolin test).

In addition, all patients had a complete ear-nose-throat (ENT) evaluation which included: 1) a specific medical questionnaire for ear involvement, 2) ENT

From the ENT Department and the Division of Rheumatology*, Department of Internal Medicine, Medical School, University of Ioannina, Greece.
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examination, 3) audiological examination. This was carried out by the same investigators and included: 1) Pure tone audiometry (i. air conduction thresholds at octave frequencies from 250 to 8000 Hz, ii. bone conduction thresholds at octave frequencies from 250 to 4000 Hz). (2) Impedance audiometry (i. tympanogram, according to Jerger's types, ii. acoustic reflexes as follows: a) measurement of acoustic reflex threshold at octave frequencies from 500 to 4000 hz ipsi and contra, b) measurement of reflex decay for the frequencies of 500 and 1000 Hz contra. (3) Speech audiometry (i. speech reception threshold and ii. speech recognition score). (4) Auditory brainstem response when retrocochlear damage was suspected.

For audiological evaluation the following devices were used: a) two channel audiometer (type Amplaid 450); b) impedance audiometer (type Amplaid 720); c) sound proof chamber (type Amplaid); and d) Biologic traveler ABRs. Patients with a congenital hearing loss, congenital anatomical abnormalities of the head and neck, skull or neck trauma, noise-induced hearing loss, acoustic trauma, otorrhoea, use of drugs known to cause ototoxicity (such as salicylates and streptomycin) were excluded from the study.

In addition, 50 healthy women matched for age, with no history of congenital hearing loss, congenital anatomical abnormalities of the head and neck, skull or neck trauma, noise-induced hearing loss, acoustic trauma, otorrhoea, use of drugs known to cause ototoxicity, were selected from hospital personnel and healthy blood donors and used as the control group. The above investigational protocol has been approved by the local ethical committee and all patients and controls had an informed consent.

Since age can influence the results, for more reliable comparisons, we divided our patients and controls into five groups according to their age: group A (age 25–34 years), group B (age 35–44 years), group C (age 45–54 years), group D (age 55–64 years) and group E (age 65–73). A patient was considered to have abnormal hearing, if at any frequency, the hearing threshold was 20 dB HL or more above the mean of the control individuals of the age group.

The statistical analysis was performed using Contingency tables with Fischer's exact and Mann-Whitney test when indicated.

Results

From the 43 screened SLE patients five have been excluded, three because of noise-induced hearing loss and two because of chronic use of salicylates. Thus the results referred to 38 patients.

The demographic, clinical, immunological and therapeutic findings of our patients are depicted in Table I. According to the age distribution, six patients belonged to group A, 10 to group B, nine to group C, nine to group D and four to group E. Respectively the distribution of controls were: eight in group A, nine in group B, 11 in group C, 11 in

TABLE I
CLINICAL, IMMUNOLOGICAL AND DRUG THERAPY IN 38 SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

Parameters	n	%
Mean age (× ± SD) (years)	47.86 ± 12.69	
Frequency distribution of age		
group A (25–34 years)	6	15.78
group B (35–44 years)	10	26.316
group C (45–54 years)	9	23.684
group D (55–64 years)	9	23.684
group E (65–73 years)	4	10.526
Mean disease duration (× ± SD)	11.76 ± 6.20	
Systemic manifestations of SLE patients:		
Raynaud's phenomenon	10	26.3
Skin vasculitis	5	13.15
CNS involvement	1	2.63
Kidney involvement	2	5.26
Immunological		
Antinuclear antibodies	32	84.2
Ro(SSA)	9	23.6
ds–DNA (high)	16	42.10
Sm	4	10.52
aCL (IgG)	4	10.52
aCL (IgM)	3	7.89
LAC	1	2.63
C3 (low)	3	7.89
C4 (low)	20	52.63
Drug therapy		
Steroids	24	63.15
Hydroxycloroquine	10	26.3
Nifedipine	5	13.15
Azathioprine	2	5.26
Cyclosporine–A	2	5.26
Methotrexate	1	2.63
NSAIDs	1	2.63

SLE = systemic lupus erythematosus; CNS = central nervous system; aCL = anticardiolipin antibodies; LAC = lupus anticoagulant; NSAIDs = non-steroidal anti-inflammatory drugs.

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TABLE II
COMPARISON OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH AND WITHOUT HEARING LOSS

Variables–Parameters	Patients with HL (n = 9)	Patients without HL (n = 29)	*p*
Mean age (× ± SD) (years)	53.4 ± 9.04	46.138 ± 13.285	0.1066
Mean disease duration (× ± SD)	11.44 ± 7.12	11.86 ± 6.028	0.7185
Systemic manifestations of SLE patients			
Raynaud's phenomenon	2	8	>0.9999
Skin vasculitis	2	3	0.5741
CNS involvement	0	1	>0.9999
Kidney involvement	1	1	0.4225
Immunological			
Antinuclear antibodies	9	23	0.3031
Ro(SSA)	3	6	0.6553
ds–DNA (high)	3	13	0.7060
Sm	0	4	0.5545
aCL (IgG)	2	2	0.2327
aCL (IgM)	2	1	0.1337
LAC	1	9	0.2368
C3 (low)	0	3	0.5669
C4 (low)	5	15	>0.9999
Drug therapy			
Steroids	8	16	0.1147
Hydroxychloroquine	3	7	0.6731
Nifedipine	2	3	0.5741
Azathioprine	0	2	>0.999
Cyclosporine–A	1	1	0.4225
Methotrexate	1	0	0.2368
NSAIDs	0	1	>0.9999

HL = hearing loss; CNS = central nervous system; aCL = anticardiolipin antibodies; LAC = lupus anticoagulant; NSAIDs = non-steroidal anti-inflammatory drugs

group D and 11 in group E. Skin vasculitis was found in five patients. Ten had Raynaud's phenomenon, two kidney involvement, one CNS involvement and none peripheral neuropathy. Antinuclear antibodies were found in 84.2 per cent of patients, Ro(SSA) in 23.6 per cent, while aCL(IgM) antibodies were found in 10.52 per cent and aCL(IgM) antibodies in 7.89 per cent of our patients. Furthermore four patients had Sm antibodies, 16 patients had high levels of ds-DNA antibodies, while 7.89 per cent of the patients had low C_3 and 52.63 per cent low C_4 complement levels.

Pure tone audiometry revealed SNHL in eight patients (21.05 per cent) and CHL in one patient (2.63 per cent). The distribution of them in the age groups was as followed: two patients in group B, three patients in group C, three patients in group D, and one patient in group E. There were no statistically significant differences (SSD) between patients with HL, and those without, regarding mean age, clinical manifestations, autoantibody profile, disease duration and drug therapy (Table II).

From these nine patients, only one had bilateral symmetric SNHL. The audiometric configuration of this patient was essentially flat (sloped at frequency of 8000 Hz) and the degree of SNHL was moderate for the frequencies from 250 to 4000 Hz (50–60 dB HL) and severe for the frequency of 8000 Hz (70–80 dB HL). Four patients (10.52 per cent) had bilateral but asymmetric SNHL. The audiometric configuration of one of them sloped only at high frequencies (4000–8000 Hz), while the remaining three patients had asymmetric flat audiometric configuration which sloped at high frequencies (4000–8000 Hz). One patient had unilateral CHL (left ear). Finally, three patients showed unilateral SNHL. The audiometric configuration of one of them was flat, while the remaining two patients had high frequency hearing loss (Table III).

Five out of nine SLE patients with HL (55.5 per cent) had low C_4 levels while three out of nine SLE patients with HL had high levels of ds-DNA (33.3 per cent). Simultaneously low C_4 and high levels of ds-DNA was noticed in 10 patients but concomitant SNHL was observed in only two of them.

The absolute values of the mean ±1 standard deviation (SD) of the hearing thresholds of patients and controls in dB HI at the serial frequencies are presented in Table IV.

Middle-ear pressure was normal in all patients and all controls. The types of tympanograms of SLE patients are depicted in Table V. No SSD in mean static compliance value was found between SLE patients and the controls. In almost all SLE patients acoustic reflexes were presented within normal limits, contra and ipsi, the only exception being the patient with the CHL (acoustic reflexes could not be elicited unilaterally).

No positive reflex decay was found.

TABLE III
DESCRIPTION OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH HEARING LOSS

Frequency distribution for side (ear)	Number of patients	%
Right	6	15.78
Left	8	21.05
Right only	1	2.63
Left only	3	7.89
Both (right and left)	5	13.15

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TABLE IV
MEAN ± 1 SD OF THE HEARING THRESHOLDS OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND CONTROLS IN DB HL

Patients	Frequencies (right ears only)					
	250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz
Group A						
Controls	11.2 ± 4.4	11.2 ± 4.4	10 ± 3.7	9.3 ± 4.9	11.2 ± 5.8	15.6 ± 11.1
SLE	11.6 ± 5.1	7.5 ± 2.7	9.1 ± 3.7	8.3 ± 4	14.1 ± 9.1	17.5 ± 10.3
Group B						
Controls	13.8 ± 4.8	15.5 ± 5.8	11.1 ± 4.1	8.8 ± 7.8	15 ± 5	20 ± 7
SLE	17.5 ± 5.4	13.5 ± 5.7	11.5 ± 6.6	9 ± 6.5	14 ± 6.5	22.5 ± 9.2
Group C						
Controls	18.1 ± 6.0	17.7 ± 6.8	17.2 ± 6	14.5 ± 5.6	18.6 ± 6.7	28.6 ± 9.2
SLE	16.6 ± 8.2	15 ± 8.2	15.5 ± 7.2	12.2 ± 7.9	20 ± 6.6	28.8 ± 17.6
Group D						
Controls	19 ± 5.8	19.5 ± 5.6	21.36 ± 5.5	19.5 ± 5.6	25.9 ± 5.8	38.1 ± 11
SLE	16.1 ± 4.8	15.5 ± 7.6	16.1 ± 9.2	17.7 ± 11.2	26.1 ± 13.6	50.5 ± 25.5
Group E						
Controls	26.3 ± 7.4	27.2 ± 7.5	20.9 ± 4.9	27.2 ± 9.5	36.3 ± 9.5	47.7 ± 8.4
SLE	23.7 ± 14.9	25 ± 19.5	31.2 ± 17.9	25 ± 15.8	32.5 ± 15.5	57.5 ± 27.2

SLE = systemic lupus erythematosus

Speech audiometry showed discrimination scores compatible with cochlear disease. None of the patients underwent ABR evaluation because in none of them was a retrocochlear lesion suspected.

Discussion

HL has been reported in many auto-immune rheumatic diseases (ARD) but the prevalence and the frequency of such disorders varies among the investigators.[1,11–17] However, studies from our group showed a relatively low prevalence of HL in rheumatoid arthritis,[14] Sjögren's syndrome[16] and scleroderma patients.[17] Concerning the pathogenesis of HL in ARD, it is still unknown whether the same disease process, or the presence of autoantibodies, or even the immunosuppressive drug therapy are responsible for it. SLE is the prototype of auto-immune disease characterized by B-cell hyperactivity, a plethora of autoantibody production, that results in IC formation, leading to tissue damage.[1–3,18] The cellular pathology of the disease in lupus patients can be classified into two broad categories: inflammatory and thrombotic. The former may, or may not be, associated with local deposition of IC and the latter is associated with the presence of antiphospholipid antibodies.[18–21]

HL has been reported occasionally in SLE patients.[6,8,9] Moreover, a few cases of sudden profound SNHL as the initial symptom of SLE have also been reported.[7,22–25]

Andonopoulus *et al.* in a controlled study showed that 23 out of 40 SLE patients (57.5 per cent) had impaired hearing, which was not associated with the presence of vasculitis, other disease systemic manifestations, or with the presence of anti ds-DNA antibodies. They concluded that these findings are probably attributed to a possible subclinical cochlear hydrops.[6] However, pathology findings from autopsies of temporal bones from SLE patients showed that only one of seven patients with HL had unilateral cochlear hydrops.[26]

In the present study HL was found in nine out of 40 patients (22.5 per cent). From these, eight patients had SNHL and only one had CHL. This prevalence is much lower than that reported by others.[6] The acoustic reflex thresholds were within normal limits in all patients with SNHL and the reflex decay was also normal (both findings also indicated cochlear lesion). Speech discrimination scores were also compatible with cochlear disease. No SSD were found between the two groups, those with and those without HL, concerning disease duration, disease activity, other systemic disease manifestation and drug therapy. In addition, no SSD were found between the two groups as regard the immunological profile. Thus, the possibility of inner ear damage due to autoantibody activity has not been demonstrated in our study. Similarly, HL in our patients does not seem to correlate with low complement levels (C_3 and C_4) and high levels of ds-DNA antibodies or even with the presence of antiphospholipid antibodies. Certainly our sample was relatively small, so

TABLE V
TYPES OF TYMPANOGRAMS OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS ENTERED TO THE STUDY

Type	Right ears		Left ears	
	Frequency	Percent	Frequency	Percent
A	35	92.10	34	89.47
As	2	5.26	3	7.89
Ad	1	2.63	1	2.63
Total	38	100	38	100

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a type II error (missed significant difference) could be present. Finally, the possibility of subclinical hydrops in SLE patients has not been verified in our study, contrary to the observation of Andonopoulos *et al*.[6] Moreover, our results are in agreement with the autopsy finding of 14 temporal bones of patients with SLE in which cochlear hydrops was found in only one ear, while in most cases various degree of hair cell loss, atrophy of the stria vascularis and loss of spiral ganglion cells were found.[26]

In conclusion, HL was found in about one fourth of our SLE patients. The majority of patients had a SNHL affecting the middle and mainly the high frequencies, while only one patient had CHL. SNHL may be bilateral (symmetric or not) or unilateral. It seems that the mechanisms of inner ear damage in SLE are still unknown and many factors are probably responsible for it. Thus, additional prospective studies are needed to elucidate its pathogenesis.

References

1 Christian CL, Elkon KB. Autoantibodies to intracellular proteins. Clinical and biological significance. *Am J Med* 1986;**80**:53–61
2 Van Venrooij WJ, Sillekens PT. Small nuclear RNA associated proteins: autoantigens in connective tissue diseases. *Clin Exp Rheumatol* 1989;**7**:635–45
3 Mohan C, Datta SK. Lupus key pathogenic mechanisms and contributing factors. *Clin Immunol Immunopathol* 1995;**77**:209–20
4 Boumpas DT, Austin HA, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 1: Renal, neuropsychiatric, cardiovascular pulmonary and hematologic disease. *Ann Intern Med* 1995;**122**:940–50
5 Boumpas DT, Fessler BJ , Austin HA, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 2: Dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. *Ann Int Med* 1995;**123**:42–53
6 Andonopoulos AP, Naxakis S, Goumas P, Lygatsikas C. Sensorineural hearing disorders in systemic lupus erythematosus. A controlled study. *Clin Exp Rheumatol* 1995;**13**:137–41
7 Caldarelli DD, Rejowski JE, Corey JP. Sensorineural hearing loss in lupus erythematosus. *Am J Otol* 1986;**7**:210–3
8 Bowman CA, Linthicum FH, Nelson RA, Mikami K, Quismorio F. Sensorineural hearing loss associated with systemic lupus erythematosus. *Otolaryngol Head Neck Surg* 1986;**94**:197–204
9 Sperling NM, Tehrani K, Liebling A, Ginzler E. Aural symptoms and hearing loss in patients with lupus. *Otolaryngol Head Neck Surg* 1998;**118**:762–5
10 Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield UF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–7
11 Heyworth T, Liyanage SP. A pilot survey of hearing loss in patients with rheumatoid arthritis. *Scand J Rheumatol* 1972;**1**:81–3
12 Goodwill CJ, Lord IJ, Knill Jones RP. Hearing in rheumatoid arthritis. A clinical and audiometric survey. *Ann Rheum Dis* 1972;**31**:170–3
13 Magaro M, Zoli A, Altomonte L, Mirone L, Corvino G, Girolamo S, *et al*. Sensorineural hearing loss in rheumatoid arthritis. *Clin Exp Rheumatol* 1990;**8**:487–90
14 Kastanioudakis I, Skevas A, Danielidis V, Tsiakou E, Drosos AA, Moutsopoulos HM. Inner ear involvement in rheumatoid arthritis: a prospective clinical study. *J Laryngol Otol* 1995;**109**:713–8
15 Kornblut AD, Wolff S, Fauci AS. Ear disease in patients with Wegener's granulomatosis. *Laryngoscope* 1982;**92**:713–7
16 Ziavra N, Politi EN, Kastanioudakis I, Skevas A, Drosos AA. Hearing loss in Sjögren's syndrome patients. A comparative study. *Clin Exp Rheumatol* 2000;**18**:725–8
17 Kastanioudakis I, Ziavra N, Politi EN, Exarchakos G, Drosos AA, Skevas A. Hearing loss in progressive systemic sclerosis patients: A comparative study. *Otolaryngol Head Neck Surg* 2001;**124**:522–5
18 Belmont HM, Abramson SB, Lie JT. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Interactions of inflammatory cells and activated endothelium. *Arthritis Rheum* 1996;**39**:9–22
19 Lie JT. Vasculopathy in the antiphospholipid syndrome: thrombosis or vasculitis, or both? *J Rheumatol* 1989;**16**:713–5
20 Lie JT. Vasculitis in the antiphospholipid syndrome: culprit or consort? *J Rheumatol* 1994;**21**:397–9
21 Lie JT, Kobayashi S, Tokano Y, Hashimoto H. Systemic and cerebral necrotizing vasculitis coexisting with disseminated coagulopathy in systemic lupus erythematosus associated with antiphospholipid syndrome. *J Rheumatol* 1995;**20**:2173–6
22 Vyse T, Luxon LM, Walport MJ. Audiovestibular manifestations of the antiphospolipid syndrome. *J Laryngol Otol* 1994;**108**:57–9
23 Naarendorp M, Spiera H. Sudden sensorineural hearing loss in patients with systemic lupus erythematosus or lupus-like syndromes and antiphospholipid antibodies. *J Rheumatol* 1998;**25**:589–92
24 Hisashi K, Komune S, Taira T, Uemura T, Sadoshima S, Tsuda H. Anticardiolipin antibody-induced sudden profound sensorineural hearing loss. *Am J Otolaryngol* 1993;**14**:275–7
25 Kataoka H, Takeda T, Nakatani H, Saito H. Sensorineural hearing loss of suspected autoimmune etiology: a report of three cases. *Auris Nasus Larynx* 1995;**22**:53–8
26 Sone M, Schachern PA, Paparella MM, Morizono N. Study of systemic lupus erythematosus in temporal bones. *Ann Otol Rhinol Laryngol* 1999;**108**:338–44

Address for correspondence:
Ioannis Kastanioudakis, M.D.,
Assistant Professor of Otolaryngology,
Department of Otolaryngology,
Medical School, University of Ioannina,
451 10 Ioannina, Greece.

Fax: +306510 97013
E-mail: adrosos@cc.uoi.gr/otorl@cc.uoi.gr

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