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Cochlear involvement in patients with systemic autoimmune rheumatic diseases: a clinical and laboratory comparative study

Georgios K. Tsirves[1] · Paraskevi V. Voulgari[2] · Eleftherios Pelechas[2] · Asimakis D. Asimakopoulos[3] · Alexandros A. Drosos[2]

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Abstract

Purpose Inner ear involvement has been reported in systemic rheumatic disease while detection of cochlin-specific antibodies has been reported in patients with idiopatic sensorineural hearing loss, suggesting cochlin's strong link to autoimmune hearing loss. The aim of this cross-sectional study was to calculate the prevalence of sensorineural hearing loss (SNHL) in patients with systemic rheumatic diseases, and to investigate any potential correlation with human antibodies to cochlin.

Methods Patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) and systemic sclerosis (SSc) according to the criteria of American College of Rheumatology were included in the study. All patients underwent a complete ear-nose-throat physical examination and audiological evaluation with pure tone audiometry and impedance audiometry. Pure tone average was calculated, taking as a starting point the hearing loss in dB according to the recommendation 02/1 of "Bureau International d' Audiophonologie" (BIAP) so as an average hearing threshold value. Sera of all patients were tested for the presence of IgG antibodies to human cochline (COCH-IgG). Sex and age-matched healthy subjects were included as controls to each group.

Results A total of 133 patients were studied; 60 with RA, 41 with SLE, 24 with SS and 8 with SSc. 61.4% of patients reported vertigo, 41% hyperacousis, 39% hearing loss, 38% tinnitus, 37.9% headache and 2.1% sensation of ear pressure with unremarkable otoscopy. The prevalence of SNHL calculated for patients affected by RA, SLE, SS and SSc was 66.6%, 31.71%, 54.17%, and 75% respectively. The calculated average hearing thresholds value in RA was increased in comparison to SLE ($p < 0.05$). In addition it was also higher in patients with RA and secondary SS, in comparison to RA patients ($p > 0.05$). There was statistically significant correlation of average hearing threshold with disease activity score 28 (DAS28) in RA, but no correlation observed with disease activity index (SLEDAI) in SLE. COCH-IgG antibodies were detected in only two samples. The results were compared with those of their respective sex and age-matched healthy subjects.

Conclusion Our study revealed increased prevalence of SNHL in patients with systemic autoimmune rheumatic disease but no correlation of hearing loss with COCHIgG antibodies. The mechanism of inner ear damage remains unknown; thus, additional prospective studies will be needed to elucidate its pathogenesis.

Keywords Sensorineural · Hearing loss · Cochlin · Rheumatoid arthritis · Systemic lupus erythematus · Sjogren · Systemic sclerosis · Autoimmune

Introduction

Inner ear involvement has been reported in many autoimmune rheumatic diseases, including rheumatoid arthritis (RA) [1–4], systemic lupus erythematosus (SLE) [5–7], Sjogren's syndrome (SS) [8–10] and systemic sclerosis (SSc) [11, 12]. The cause and pathogenesis remain unknown. However, excessive autoantibody production might have an important role. Some of those autoantibodies cause cytotoxic damage, while others participate in immune complex

✉ Georgios K. Tsirves
tsirvesgeorgios@gmail.com

[1] Department of Otolaryngology, University Hospital of Ioannina, Leof. Stavrou Niarchou, 45500 Ioannina, Greece

[2] Department of Rheumatology, University Hospital of Ioannina, Ioannina, Greece

[3] Department of Otolaryngology, Hospital Center of Luxembourg, Luxembourg, Luxembourg

formation resulting in immune inflammation [13–15]. On the other hand autoimmune inner ear disease (AIED), was first described by Cogan in the 1940s and Lehnhardt in the 1950s, and a limited series of patients benefitted from a combination of steroids and cyclophosphamide, as noted by McCabe in the 1970s. Described by investigators as a bilateral SNHL with a decline in at least one ear evolving in greater than 3 days (to distinguish by suddent SNHL) but less than 90 days (to distinguish by presbycusis). The incidence of AIED is estimated to be less than 5 in 100,000 and represents less than 1% of all SNHL [16]. As with most autoimmune diseases, it has been postulated that a misdirected attack of self, in this case to inner ear proteins, results in both proinflammatory T-cell responses and autoantibody formation, which represent the basic features of AIED. Immunology of the inner ear is difficult to investigate due to inaccessibility of the tissue in human disease. Cochlin is a promising candidate for evaluation as its expression is predominantly confined to the inner ear, where it is present abundantly and has been suggested to have important roles in the homeostasis of the vestibule together with collagen II. Cochlin may also have a role in AIED as anti-cochlin antibodies and T-cells specific for cochlin have been detected in these patients, suggesting an active immune response to this protein [17]. This prompted us to investigate the presence of hearing loss in systemic autoimmune rheumatic disease patients and to determine the factors that might be implicated in its pathogenesis, including correlation with IgG antibodies to human cochlin (COCH-IgG).

Materials and methods

A total of 133 consecutive, unselected, adult patients followed-up at the Rheumatology outpatient clinics of Ioannina University Hospital, who were diagnosed with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) and systemic sclerosis (SSc) and fulfilled the criteria of American College of Rheumatology for the respective diagnosis, were included in the analysis.

Exclusion criteria

Patients with a history of congenital hearing loss, anatomical abnormalities of the head and neck, skull or neck trauma, middle ear surgery, otorrhoea, Meniere's disease, exposure to noise or using ototoxic drugs (i.e. high dose of salicylate, streptomycin, etc) were excluded from the study.

In addition a total of 133 age- (± 2 years) and sex-matched healthy individuals, without a history of ear disease, were used for the four control groups. The patients who entered the study had a complete physical and laboratory evaluation. All systemic manifestations, as well as the current treatment, were recorded. All patients had a complete ear-nose-throat evaluation that included: (1) a specific medical questionnaire for ear involvement, (2) ear-nose-throat examination, including otoscopy with surgical microscope and nasendoscopy, (3) audiological examination. This has been performed by the same investigator and included:

- Pure tone audiometry (air conduction thresholds at octave frequencies from 250 to 8000 Hz; bone conduction thresholds at octave from 250 to 4000 Hz).
- Impedance audiometry (tympanogram according to Jerger's types and measurement of acoustic reflex threshold at octave frequencies from 500 to 4000 Hz ipsilateral and contralateral).

For the audiological evaluation the following devices were used: (1) 2-channel audiometer (type Amplaid 450), (2) impedance audiometer (type Amplaid 720) and (3) soundproof chamber (type Amplaid). To quantify hearing impairment and also compare the results we decided to avoid arithmetic average for each frequency separately. A pure tone average (PTA) thresholds value was calculated for each ear, as the numerical mean of the frequencies 500, 1000, 2000 and 4000 Hz as by recommendation 02/1 bis of Bureau International d`Audiophonologie (BIAP) [18]. PTA values were expressed in decibels hearing level (dB HL). Normal or subnormal hearings were considered for thresholds 20 dB HL or lower. Thresholds between 21 and 40 dB HL were considered as mild hearing impairment; between 41 and 70 dB HL, moderate; between 71 and 90 dB HL, severe; and between 91 and 119 dB HL, very severe hearing loss. Patients with thresholds of 120 dB HL or higher were classified as profound hearing loss-cophosis. The audiometric configurations of the audiogram were classified according Carhart as either horizontal, slightly descending, sharply descending, descending sloping, ascending, notch, U-shape, inverted U or atypical [19]. Also an average hearing loss value (AHLV) was calculated from the above PTAs, for each ear, on every disease subgroup and their corresponding controls. The presence or absence of contralateral stapedius reflex was also analysed. It was considered normal if the acoustic stapedius reflex threshold was 70–90 dB HL higher than the pure-tone threshold calculated on the same frequency. On the other hand, Metz recruitment phenomenon [20] was considered positive when the difference between the pure-tone threshold and the reflex threshold value was equal to or lower than 60 dB HL.

Before entry, all patients had a laboratory and immunological evaluation which included: complete blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factor (RF) (latex test), antinuclear antibodies (ANA) (indirect immunofluorescence), antibodies to Ro (SSA), La (SSB), U1RNP and Scl70

(immunoblot), anticardiolipin antibodies (aCL) and anti-cyclic citrullinated peptide (anti-CCP) antibodies (ELISA) as well as C3 and C4 complement levels. Disease Activity Score 28 (DAS28) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were calculated for patients with RA and SLE, respectively. The sera of all patients was tested (ELISA) for presence of IgG for human cochlin (COCH-IgG) using MyBioSourse's kit (Cat. No: MBS108983). The above investigational protocol has been approved by the local ethical committee, and informed consent was obtained from all individual participants included in the study.

Statistical analysis

Mean values and standard deviations were used to describe scale measurements and frequencies to describe categorical ones. Normality tests with the Shapiro–Wilk criterion were applied where applicable to determine the choice of statistical tests. The Paired samples *t* test was used to assess differences between right ear and left ear for each patient, and the Independent samples *t* test for separate groups of patients. When testing for differences in the outcome measures in more than two groups the Analysis of Variance method was applied followed by multiple comparisons with the Tukeys' HSD criterion. The Spearman's correlation coefficient was used to assess the correlation between DAS 28 and BIAP measurements. Statistical significance was set at 0.05 in all cases. All results were produced with the use of IBM SPSS Statistics software v22.0.

Results

We studied 133 patients: 60 with RA (including 4 with secondary SS), 41 with SLE, 24 with primary SS and 6 with SSc. The demographic characteristics and ESR average of our patients are depicted in Table 1. The specific medical questionnaire for ear involvement revealed 61.4% vertigo, 41% hyperacousis, 39% hearing loss, 38% tinnitus, 37.9% headache and 2.1% sensation of ear pressure with unremarkable otoscopy. Table 2 depicts the mean of air bone conduction thresholds by frequency in each ear and in every group. The analysis of the audiometric configuration of the audiograms according to Carhart in the majority of the cases, is all four conditions, had a U-shape revealing that the middle frequencies were more affected. Impedance audiometry revealed 125 type-A curves bilaterally and 8 type-C1 curves bilaterally. In 13 patients stapedial reflex was absent, while Metz phenomenon was positive in 22 patients (36.66%) with RA, in 9 (21.95%) with SLE, in 6 (25%) with SS and in 4 (50%) with SSc. The PTA value calculated for each ear of the patients revealed that the prevalence of sensorineural hearing loss was increased in patients affected by systemic autoimmune rheumatic diseases in comparison to the healthy control individuals. According BIAP 02/1 bis within the RA group, 40/60 (66.6%) patients had sensorineural hearing loss: 10 patients had mild unilateral and 30 patients bilateral hearing loss (18 mild and 12 moderate). Within the SLE group 13/41 (31.71%) patients had sensorineural hearing loss: six patients had mild unilateral and 7 had bilateral heaving loss (5 mild and 2 moderate). Within SS group, it was found that 13/24 (54.17%) patients had sensorineural hearing loss (2 patients had mild unilateral and 11 patients mild bilateral). Finally, within the SSc group 6/8 (75%) patients had sensorineural hearing loss: 3 patients had mild unilateral and another 3 patients had bilateral (2 mild and 1 moderate). In 6 patients, because of a greater than 10 dB HL asymmetry between the two ears, an MRI with gadolinium of the internal auditory canals was performed, excluding a retrocochlear lesion. For each disease group, including their corresponding controls, an average hearing loss value (AHLV) was calculated, as the arithmetic mean of the PTAs (Table 3). This AHLV for patients with RA, SLE and SS was found to be increased in comparison to healthy controls ($p < 0.05$). The value calculated for patients with SSc was increased in comparison to their healthy controls, but not statistically significant (Table 3). The increased AHLV calculated in RA patients was statistically significant ($p < 0.05$) in comparison to SLE patients, and whilst it was increased also in patients with RA and secondary SS in comparison to patients affected by RA, this was not statistically significant ($p > 0.05$). Spearman's correlation coefficient revealed a statistically significant correlation between DAS28 and AHLV

Table 1 Demographic findings of the patients entered in the study

	RA	SLE	SSc	SS
Gender F/M	49/11	34/7	6/2	24/0
Age: years (SD) Female	64.63 (10.49)	49.06 (15.52)	70.83 (7.88)	62.13 (12.18)
Age: years (SD) Male	62.27 (18.61)	53.43 (10.34)	62 (12.73)	n/a
Disease duration: years (SD)	13.53 (9.71)	15.32 (10.15)	13.38(12.18)	13.63 (9.67)
ESR (SD)	30.05 (21.699)	20.71 (16.208)	29.103 (9.891)	23.13 (17.826)

Table 2 Mean of air conduction thresholds by frequency in each ear and in every disease group

	Diagnosis							
	RA		SLE		SSc		SS	
	Status		Status		Status		Status	
	Control	Case	Control	Case	Control	Case	Control	Case
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Right 250 Hz	15.00	26.25	15.37	22,20	20.00	28.13	17.50	26.46
Right 500 Hz	14.17	24.42	14.51	20.98	17.50	25.63	15.42	25.00
Right 1000 Hz	12.58	19.33	10.85	15.24	11.88	16.88	11.25	16.46
Right 2000 Hz	17.00	22.25	11.10	15.61	20.00	19.38	12.29	19.17
Right 3000 Hz	22.33	28.08	13.29	18.05	23.75	21.88	17.29	23.13
Right 4000 Hz	27.42	34.58	17.44	20.73	30.63	31.88	23.54	29.79
Right 8000 Hz	35.58	41.50	20.61	22.44	36.25	51.88	29.38	38.96
Left 250 Hz	13.92	25.83	15.73	21.71	20.00	26.25	16.25	27.50
Left 500 Hz	15.25	26.00	15.37	21.83	18.75	25.00	17.71	26.46
Left 1000 Hz	12.33	20.92	12.20	15.85	15.00	19.38	12.50	18.13
Left 2000 Hz	17.33	23.83	12.07	15.24	16.25	21.88	14.38	21.04
Left 3000 Hz	22.75	29.67	14.51	18.78	23.75	31.88	18.75	25.63
Left 4000 Hz	27.25	34.50	16.83	20.73	30.00	38.75	23.96	27.71
Left 8000 Hz	36.92	43.08	22.68	25.00	36.88	51.88	32.92	40.21

Table 3 Average hearing loss value (AHLV) calculated using PTAs in systemic autoimmune rheumatic disease and difference from healthy controls with statistical correlation

	N	Mean	Std. deviation	Std. error	95% confidence interval for mean		Minimum	Maximum	Mean difference from control	Sig. (2-tailed)
					Lower bound	Upper bound				
Right ear										
RA	60	25.1458	12.16956	1.57108	22.0021	28.2896	5.00	57.50	7.35417	0.000
Control	60	17.7917	5.76447	0.74419						
SLE	41	18.1402	10.03946	1.56790	14.9714	21.3091	6.25	51.25	4.66463	0.002
Control	41	13.4756	2.24465	0.86593						
SSc	8	23.4375	9.81412	3.46982	15.2327	31.6423	12.50	41.25	3.43750	0.359
Control	8	20.0000	5.46907	1.93361						
SS	24	22.6042	8.65175	1.76603	18.9509	26.2575	8.75	43.75	6.97917	0.000
Control	24	15.6250	5.74598	1.17289						
Left ear										
RA	60	26.3125	13.00755	1.67927	22.9523	29.6727	5.00	58.75	8.27083	0.000
Control	60	18.0417	5.83298	0.75303						
SLE	41	18,4146	10.63244	1.66051	15.0586	21.7706	7.50	56.25	4.29878	0.003
Control	41	14.1159	5.09476	0.79567						
SSc	8	26,2500	9.81981	3.47183	18.0404	34.4596	16.25	42.50	6.25000	0.112
Control	8	20.0000	5.59017	1.97642						
SS	24	23.3333	9.28611	1.89552	19.4122	27.2545	8.75	40.00	6.19792	0.002
Control	24	17.1354	5.60812	1.14475						

of both ears in RA (Table 4), but no correlation with SLEDAI that represents the index of disease activity for SLE. There was no statistically significant correlation between AHLV and gender, disease duration, ESR, RF, complement factors C3/C4, ANA, aCL, antibodies to Ro(SSA), La(SSB) or anti-CCP for any of the groups. RF positivity was associated with higher AHLVs within the SLE group but was not statistically significant ($p = 0.332$ and 0.330).

Table 4 Spearman correlation coefficient of AHLV with DAS28 and SLEDAI

	DAS28	BIAP_D	BIAP_S
Spearman's rho			
DAS28			
Correlation coefficient	1.000	0.301	0.315
Sig. (2-tailed)		0.019	0.014
N	60	60	60
	SLEDAI	BIAP_D	BIAP_S
Spearman's rho			
SLEDAI			
Correlation coefficient	1.000	− 0.229	− 0.173
Sig. (2-tailed)		0.149	0.215
N	41	41	41

Medications used in our patients' treatment included synthetic disease-modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine, methotrexate, cyclosporine, azathioprine, mycophenolate mofetil or leflunomide, biological factors such as tocilizumab, infliximab, certolizumab, adalimumab or etanercept, and corticosteroids. Twelve patients received no treatment during evaluation while most of the patients received a combination of two or three disease-modifying anti-rheumatic drugs (DMARDs). Ten patients received low dose of salicylate. To analyze the impact of medical treatment on the pathogenesis of sensorineural hearing loss and compare the data we considered the following subgroups: no treatment (12 patients), only synthetic DMARDs (40 patients), treatment with biologic factors (16 patients), only corticosteroids (7 patients), synthetic DMARDs with corticosteroids (45 patients) and other combinations (13 patients). Within the RA group, patients receiving TNF-inhibitors had a lower AHLV (Table 5) but the difference was not statistically significant (Table 6) as the p values were 0.257 and 0.411 for the right and left ears, respectively. Within the SLE group, patients receiving synthetic DMARDs and corticosteroids had a higher AHLV (Table 5) but again the difference was not statistically significant (*p* values 0.377 and 0.897 for right and left ears, respectively). Within the SS group, patients receiving only synthetic DMARDs had lower AHLV but with p values of 0.142 and 0.395 for the right and left ears, respectively. Finally, there was no statistically significant difference within any subgroup for the patients receiving low dose of salicylate. Notice here that because of the small number of patients in the SSc group, it was not possible to elaborate any data into subgroups of different medical treatment.

Only two samples were positive for IgG-COCH, the first: a patient with RA and secondary SS with PTA of 51.85 dB HL, while the second was a patient with RA and PTA of 42.5 dB HL.

Discussion

Sensorineural hearing loss has been reported in many autoimmune rheumatic diseases but the prevalence and the frequency of such disorders vary among investigators. The inner ear damage is attributed to vasculitis or neuronitis or it may represent an ototoxic effect of the medications used in the treatment of these patients [3–7, 12, 21]. Goodwill [1] in the UK and Heyworth [1] in Sweden published the first case series of RA patients with hearing loss and since then, published data reports a prevalence of sensorineural hearing loss of 21–69.8% for RA [22], 8–28.6% for SLE [6], 21–46% for SS [23, 24] and 20–77% for SSc [25]. The calculated prevalence of hearing loss in our study was 66.6%, 31.71%, 54.17% and 75%, respectively. The positive Metz recruitment phenomenon calculated, that represent an index of cochlear lesion, support the above percentages. Using recommendation 02/1 bis of BIAP with a cutoff value of 20 dB HL, the slightly superior percentages could be justified. The BIAP criteria are more sensible to detect hearing loss in elderly subjects [26] while the average age of our patients was raised within the RA, SS, and SSc groups. In many older studies there is heterogeneity on the definition of hearing loss, while the examination of every frequency separately is not facilitating any further comparisons. The advantage of calculating AHLV from the PTAs, on each disease group separately, allows statistical comparison of these values with multiple variants independently. Statistically significant correlation of the AHLV with disease activity score DAS28 in RA group but without correlation with disease duration, could indicate that immune system's acute activity and production of pro-inflammatory cytokines that damage the inner ear cells, cause the hearing loss. In the SLE group there was no statistically significant difference between AHLV and SLEDAI, the corresponding index of disease activity, raising the suspicion for a different mechanism of inner ear

Table 5 AHLVs calculated for RA, SLE and SS patients into different medical treatment subgroups

	N	Mean	Std. deviation	Std. error	95% confidence interval for mean	
					Lower bound	Upper bound
Right ear RA subgroup						
Only synthetic	20	23.2500	11.66557	2.60850	17.7903	28.7097
Including biologic factors	16	21.9531	10.58663	2.64666	16.3119	27.5943
Synthetic and steroids	17	28.4559	13.51019	3.27670	21.5096	35.4022
Total	53	24.5283	12.08003	1.65932	21.1986	27.8580
Left ear RA subgroup						
Only synthetic	20	25.3750	13.77748	3.08074	18.9269	31.8231
Including biologic factors	16	22.5000	11.11493	2.77873	16.5773	28.4227
Synthetic and steroids	17	28.3824	12.34090	2.99311	22.0372	34.7275
Total	53	25.4717	12.54374	1.72301	22.0142	28.9292
Right ear SLE subgroup						
Synthetic	10	15.8750	6.06819	1.91893	11.5341	20.2159
Synthetic and steroids	21	19.2262	10.97210	2.39431	14.2318	24.2206
Total	31	18.1452	9.68714	1.73986	14.5919	21.6984
Left ear SLE subgroup						
Synthetic	10	17.7500	6.96718	2.20322	12.7660	22.7340
Synthetic and steroids	21	18.2738	11.72921	2.55952	12.9347	23.6129
Total	31	18.1048	10.31216	1.85212	14.3223	21.8874
Right ear SS subgroup						
No treatment	6	22.9167	6.83130	2.78887	15.7477	30.0857
Synthetic	10	18.6250	4.30802	1.36232	15.5432	21.7068
Total	16	20.2344	5.59424	1.39856	17.2534	23.2153
Left ear SS subgroup						
No treatment	6	24.7917	8.63918	3.52693	15.7254	33.8579
Synthetic	10	21.2500	7.31247	2.31241	16.0190	26.4810
Total	16	22.5781	7.75227	1.93807	18.4472	26.7090

damage in these patients, which would justify further investigation in the future. The small number of patients with RA and secondary SS pose a serious challenge to the statistical validation of the higher AHLV observed into this subgroup. There was no correlation with most of laboratory variants (RF, ANA, C3/C4, aCL, SSA/SSB, anti-CCP) and disease duration which is in accordance with most published studies.

Drug therapy was not correlated with the calculated AHLVs while the use of DMARDs did not improve the calculated thresholds as hypothesised on other studies. In our study the hearing loss seems not to be the result of ototoxicity but caused by cochlear lesions with an unknown mechanism. Cochlin is the major component of the extracellular matrix in the inner ear together with collagen [27, 28]. It is expressed in both the cochlea and the vestibule of the inner ear and is encoded by the Coagulation factor C homology gene. Defects in cochlin have been identified in the autosomal dominant non-syndromic auditory and vestibular disorder DFNA9, Meniere's disease and in presbyacusis [27, 29–31]. Detection of cochlin-specific antibodies has been reported in 14% of patients with idiopathic hearing loss [32]. Cochlin has been also shown to have a strong link to autoimmune hearing loss [17]. Autoimmune inner ear disease patients were found to have significantly higher serum levels of anti-cochlin antibodies compared to healthy controls and patients with noise- and age-related hearing loss [33]. In our study only two samples were positive for COCH-IgG and for that reason,we could exclude any potential role of cochlin in the mechanism of sensorineural hearing loss in patients with systemic rheumatic diseases.

Conclusion

In conclusion cochlea could be affected by the autoimmune process in RA, SLE, SS and SSc, putting these patients in a high-risk group for sensorineural hearing loss. Cochlin has been shown to have a strong link to autoimmune hearing loss and for that reason in our study this specific protein has been investigated for the very first time for its potential involvement to the pathogenesis of SNHL on patients with systemic rheumatoid disease. The evidence

Table 6 Statistical analysis of AHLVs calculated for RA, SLE and SS patients into different medical treatment subgroups

ANOVA					
	Sum of squares	*Df*	Mean square	*F*	Sig.
Right ear RA subgroup					
Between groups	401.026	2	200.513	1.395	0.257
Within groups	7187.182	50	143.744		
Total	7588.208	52			
Left ear RA subgroup					
Between groups	285.505	2	142.753	0.904	0.411
Within groups	7896.452	50	157.929		
Total	8181.958	52			
Right ear SLE subgroup					
Between groups	76.077	1	76.077	0.805	0.377
Within groups	2739.144	29	94.453		
Total	2815.222	30			
Left ear SLE subgroup					
Between groups	1.859	1	1.859	0.017	0.897
Within groups	3188.363	29	109.944		
Total	3190.222	30			
Right ear SS subgroup					
Between groups	69.069	1	69.069	2.415	0.142
Within groups	400.365	14	28.597		
Total	469.434	15			
Left ear SS subgroup					
Between groups	47.038	1	47.038	0.771	0.395
Within groups	854.427	14	61.031		
Total	901.465	15			

does not support the above hypothesis and the mechanism of inner ear damage on this group of patients still remains unknown. However, there is evidence from our study that in RA and SLE the mechanism might be different; thus, additional prospective studies will be needed in the future, to elucidate the pathogenesis of cochlear damage.

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Compliance with ethical standards

Research involving human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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