

Auditory function in patients with systemic lupus erythematosus

Katarzyna Maciaszczyk^{a,*}, Tomasz Durko^a, Elżbieta Waszczykowska^b, Anna Erkiert-Polguj^b,
Anna Pajor^a

^a Department of Otolaryngology, Medical University of Lodz, Barlicki University Hospital, 22, Kopcinskiego St., 90-153 Lodz, Poland

^b Department of Immunodermatology, Medical University of Lodz, 6, Krzemieniecka St., 94-015 Lodz, Poland

Received 29 December 2009; accepted 27 April 2010

Available online 23 June 2010

Abstract

Objective: Patients with systemic lupus erythematosus (SLE) may develop hearing and balance disorders as a result of the immune-mediated inner ear damage due to vasculitis or ototoxicity of drugs used in SLE treatment. The aim of the study was evaluation of the hearing organ disorders in patients with SLE with particular regard to their prevalence and relationship to duration and severity of disease. The severity was assessed from involvement of organs that resulted in poorer SLE outcome, i.e. kidneys and central nervous system (CNS), and from the presence of antibodies associated with unfavourable SLE prognosis.

Methods: Thirty-five unselected, consecutive patients (33 women, two men, mean age 47.8 years) with SLE diagnosed in compliance to the international diagnostic criteria of the American Rheumatism Association (1982) were enrolled into the study. The control group consisted of 30 otologically healthy persons matched to the SLE group for age and sex. Case history was recorded for all patients from questionnaire data and laryngological examinations were performed, followed by pure-tone, speech and impedance audiometry and auditory brainstem response audiometry (ABR).

Results: In the anamnesis 71.4% of patients reported vertigo, 62.9% headaches, 40% tinnitus, 25.7% hyperacusis, 17.1% hearing loss and 2.9% ear fullness. It was found that SLE patients had a significantly poorer mean hearing thresholds than the control group for all frequencies, except for 500; 2000 and 4000 Hz. Longer ABR latency averages were observed in the group of SLE patients compared to control. Ten patients (28.6%) developed high-frequency and symmetric sensorineural hearing loss (SNHL). Significant positive correlation between mean air-conduction hearing thresholds and SLE duration ($r = 0.46$, $p < 0.001$) was found. After taking age into consideration, hearing acuity in SLE was related to duration of disease in younger patients. Furthermore, no relation was seen between hearing level and severity of disease.

Conclusions: Auditory system involvement ought to be considered as one of elements of the clinical picture of systemic lupus erythematosus while determination of its character, original or secondary, requires further research.

© 2010 Elsevier Ireland Ltd. All rights reserved.

Keywords: Systemic lupus erythematosus; Ear; Hearing loss

1. Introduction

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease occurring all over the world with the incidence rate from 12.5 to 39 cases per 100,000 population. It is a chronic disease mostly affecting women, with periods

of exacerbations and remissions, variable in its course and prognosis [1,2]. The SLE pathogenesis is complex. Genetic, hormonal and environmental (infections, UV radiation, drugs) factors are taken into consideration in the etiology [3]. The excessive production of anti-nuclear antibodies (ANA), like dsDNA, ssDNA, Sm, RNP, Ro, La and Ku, is commonly known to take part in SLE pathogenesis. Moreover, antibodies to ribosomes, fibrillarine and RNA polymerase can be detected [1,4]. Additionally the lupus anticoagulant (LA), which is one of antibodies characteristic of anti-phospholipid syndrome, may be present in SLE, causing blood coagulation disorders and increasing the risk

* Corresponding author. Tel.: +48 42 6785 785; fax: +48 42 6785 785.

E-mail addresses: k.maciaszczyk@op.pl (K. Maciaszczyk), tomasz.durko@umed.lodz.pl (T. Durko), elzbieta.waszczykowska@umed.lodz.pl (E. Waszczykowska), aerkiert@wp.pl (A. Erkiert-Polguj), grappa@csk.umed.lodz.pl (A. Pajor).

of thrombotic complications. In SLE, circulating immune complexes causing vasculitis are deposited in internal organs and skin, producing tissue damage.

In recent years, pathological, immunological reactions have been proven to affect also the inner ear [5,6]. In the growing number of reports the sensorineural hearing loss (SNHL) is shown as one of the symptoms in autoimmune diseases of connective tissue, such as systemic sclerosis, rheumatoid arthritis, Cogan syndrome, Sjögren syndrome, Wegener's granuloma, ankylosing spondylitis and systemic lupus erythematosus [7–11].

This is why the aim of our study is assessment of hearing organ disorders in SLE patients with particular reference to their prevalence and relationship to SLE duration and severity. The severity was assessed from involvement of organs that resulted in poorer SLE outcome, i.e. kidneys and central nervous system (CNS), and from the presence of antibodies associated with unfavourable SLE prognosis.

2. Patients and methods

2.1. Characteristics of study groups

Thirty-seven unselected, consecutive patients with diagnosed SLE, who fulfilled at least four international criteria established by the American Rheumatism Association (1982), now the American College of Rheumatology [12,13], were enrolled into the study. After audiological examination, two women at the age of 54 and 60 were excluded due to the mixed hypoacusis, which could be a result of past history of chronic otitis media. A group of 33 women and two men (70 ears) were subjected to further assessment, the mean age was 47.8 ± 11.3 years (range 24–77 years). Disease duration ranged from 6 months to 33 years, the mean being 8.5 ± 8.2 years.

The control group, matched to the SLE group for age and sex, included 30 subjects (60 ears), 28 women and 2 men, ranged in age from 29 to 66 years, mean age 47.8 ± 9.8 years. The patients from control group did not report any exposure to noise, ototoxic drugs or ear diseases. They had no history of hypoacusis, tinnitus, ear fullness, vertigo, dizziness and showed no abnormalities in otolaryngologic examination.

The patients with SLE were divided according to duration of disease into three groups:

Group A: Patients suffering from SLE up to 5 years (17 subjects; mean age 42.6 years, mean SLE duration 2.7 years);

Group B: Patients suffering from SLE from 6 to 10 years (eight subjects; mean age 51.6 years, mean SLE duration 7.8 years);

Group C: Patients suffering from SLE over 10 years (10 subjects; mean age 52.8 years, mean SLE duration 19.6 years). Group A was statistically younger than groups B

($p < 0.001$) and C ($p < 0.005$), between groups B and C there was no difference as far as average age was concerned.

The SLE patients were also divided according to severity of disease evaluated as its systemic manifestations—renal involvement (R), central nervous system involvement (CNS) or presence of La, Sm, dsDNA or RNP antibodies (AB) corresponding with poor SLE prognosis.

Group R(+) consisted of seven patients (mean age 50.6 years, mean SLE duration 11.1 years) who developed proteinuria, cylindruria or autoimmune process in the kidneys confirmed by results of histological examination. Group R(–) consisted of 28 patients without renal involvement (mean age 47.1 years, mean SLE duration 7.9 years).

Group CNS(+) consisted of 9 patients (mean age – 50.1 years, mean SLE duration – 10.9 years) with psychoneurological symptoms. Group CNS(–) consisted of 26 patients (mean age 46.9 years, mean SLE duration 7.7 years) without CNS symptoms.

Group AB(+) consisted of 11 subjects (mean age 47.4 years, mean SLE duration 9.4 years) in whom La, Sm, dsDNA or RNP antibodies were detected. Group AB(–) consisted of 24 subjects (mean age 47.9 years, mean SLE duration 8.0 years), without those antibodies.

All participants were fully informed about the aim of the study and the test procedure and gave their informed consent. The Bioethics Committee of the Medical University of Lodz approved the protocol (Document No. RNR/160/07/KE).

2.2. Audiological examination

The history concerning previous otolaryngologic and internal diseases, family hearing impairment, noise exposure, ototoxic drugs, stimulants, the course, activity and medication of SLE as well as symptoms such as hypoacusis, tinnitus, vertigo, dizziness was taken by a questionnaire survey. All patients were subjected to otolaryngologic examination, including microscopic ear evaluation. Audiometric test battery, including pure-tone audiometry, speech audiometry, acoustic immittance measures and auditory brainstem response audiometry (ABR) was performed in SLE and control groups. The examination was carried out in standard sound-proof room. Pure-tone audiometry was performed for the frequencies between 125 and 8000 Hz with an Aurical clinical audiometer (Madsen, Denmark) using Telephonics TDH-39 earphones. The mean hearing loss in all SLE group, as well as in the groups compared in terms of SLE duration and severity, was calculated as arithmetical average for each of nine frequencies. The arithmetical average of hearing threshold levels for nine frequencies and values for pure-tone air conduction in at least two contiguous frequencies, both greater than 25 dB HL, were considered as hearing loss. The influence of age was taken into consideration [14,15]. Speech audiometry was performed using Pruszczyk et al. monosyllabic Polish

Table 1

Comparison of mean air-conduction thresholds (dB HL) in pure-tone audiometry between SLE group ($n = 70$ ears) and control group ($n = 60$ ears).

Frequency (Hz)	SLE group		Control group		<i>p</i>
	Range	Mean \pm SD	Range	Mean \pm SD	
125	15–35	24.5 \pm 4.4	15–30	21.3 \pm 3.8	<0.001
250	15–35	19.9 \pm 4.0	5–25	17.8 \pm 4.4	<0.05
500	10–30	18.2 \pm 4.8	5–25	16.7 \pm 4.5	ns
1000	10–35	17.4 \pm 5.6	10–20	14.2 \pm 3.5	<0.001
2000	5–40	18.5 \pm 8.0	5–25	15.3 \pm 4.5	ns
3000	5–75	22.1 \pm 13.0	5–30	16.3 \pm 6.0	<0.05
4000	5–95	23.0 \pm 15.3	5–35	17.7 \pm 7.0	ns
6000	15–100	34.6 \pm 20.4	10–40	23.5 \pm 6.8	<0.002
8000	0–85	27.8 \pm 17.9	5–40	19.5 \pm 7.8	<0.05

word test (NLA-93); the speech reception threshold (SRT) and speech discrimination score (SDS) for speech intelligibility were determined. Immittance was determined using the AZ 26 acoustic immittance bridge (Interacoustics A/S, Denmark) at a probe tone frequency of 220 Hz. In impedance audiometry type of tympanogram, the tympanic cavity pressure and the acoustic stapedial reflex threshold for pure tones (500–4000 Hz) were assessed. Auditory brainstem responses were recorded using the Navigator Pro (BioLogic, Systems Corp. USA) for 90 dB nHL click stimulus. In ABR examination morphology, the latencies for waves I, III and V and the inter-peak intervals for waves I–III, III–V and I–V were calculated.

2.3. Data analysis and statistics

Data are expressed as means \pm standard deviation (SD). In the statistical analysis, Mann–Whitney *U* test was performed for comparison of groups and Spearman's rank correlation test was employed to determine correlations between individual results. A multivariate linear regression analysis was used to estimate the relationship between the air-conduction hearing thresholds and variables like duration of disease and age. A logistic regression analysis was made to assess the relationship between hearing level and binary data (co-existing cardiovascular diseases, CNS and kidney involvement, chloroquine diphosphate and corticosteroid therapy, the presence of antibodies associated with unfavourable SLE prognosis). The differences were considered as statistically significant at *p* less than 0.05.

Table 2

Comparison of average wave latencies and inter-peak intervals (ms) in ABR between SLE group ($n = 70$ ears) and control group ($n = 60$ ears).

Parameter	SLE group		Control group		<i>p</i>
	Range	Mean \pm SD	Range	Mean \pm SD	
Latency I wave	1.44–1.94	1.68 \pm 0.13	1.5–1.83	1.63 \pm 0.08	ns
Latency III wave	3.36–4.32	3.79 \pm 0.18	3.38–3.94	3.69 \pm 0.14	<0.001
Latency V wave	5.29–6.31	5.79 \pm 0.27	5.3–6.02	5.65 \pm 0.17	<0.002
Interval I-III	1.5–2.54	2.12 \pm 0.2	1.75–2.33	2.06 \pm 0.15	ns
Interval III-V	1.5–2.36	1.99 \pm 0.21	1.66–2.37	1.96 \pm 0.14	ns
Interval I-V	3.62–4.62	4.11 \pm 0.26	3.7–4.31	4.02 \pm 0.15	<0.05

3. Results

The most frequently reported symptoms in SLE subjects were: vertigo 25 patients (71.4%) and headaches 22 patients (62.9%). Other symptoms included tinnitus 14 patients (40%), hyperacusis 9 (25.7%), hearing loss six (17.1%), balance disturbances 5 (14.3%) and ear fullness two patients (5.7%). There were no patients exposed to noise occupationally. A significant majority of patients with SLE, 30 subjects (85.7%), were treated with corticosteroids and 23 subjects (65.7%) with chloroquine diphosphate.

3.1. Comparison of audiological evaluation between the SLE and control group

The hearing thresholds in dB HL (air conduction) for the left and the right ear in both SLE and control groups did not differ significantly ($p > 0.05$), so further analysis was carried out without reference to the sides. The mean values of the air-conduction hearing thresholds in SLE patients were significantly poorer than in control group for all frequencies, except for 500; 2000 and 4000 Hz (Table 1). All SLE patients had 100% speech discrimination scores and type A tympanogram, except for one patient with type C tympanogram. Acoustic reflex showed thresholds consistent with the level of hearing loss. Speech discrimination scores reached 100% and middle-ear function was normal in all controls. In ABR examination, symmetric responses were found in all SLE patients. The average latencies were increased in the SLE patients compared with the control group. Significant differences concerned the latency of waves III and V and interval I–V (Table 2).

Table 3
Characteristics of group with SLE and hearing loss ($n = 10$ patients).

No.	Age (years)	SLE duration (years)	Chloroquine diphosphate	Steroids	Kidney	CNS	ANA	Other antibodies	Subjective symptoms				Other diseases
									Vertigo	Hearing loss	Tinnitus	Hyperacusis	
1	55	20	Yes	Yes	No	Yes	1/160	Ro, LA	Yes	Yes	Yes	Yes	Stroke
2	58	5	Yes	Yes	No	No	1/640	No	No	No	Yes	No	HA
3	66	15	Yes	Yes	No	Yes	1/640	Ro	Yes	Yes	Yes	Yes	CHD
4	55	6	Yes	Yes	No	No	1/1280	No	Yes	Yes	Yes	No	HA, DM, CHD
5	65	10	Yes	Yes	Yes	No	1/640	No	No	Yes	Yes	No	HA, CHD
6	46	20	No	Yes	No	No	1/640	No	Yes	Yes	Yes	No	No
7	53	25	Yes	No	No	No	1/320	No	Yes	Yes	No	No	No
8	58	4	Yes	Yes	No	Yes	1/640	Ro	Yes	No	No	Yes	Stroke, CHD
9	52	8	Yes	No	No	Yes	1/320	No	Yes	No	No	Yes	No
10	71	2	No	Yes	No	No	1/320	No	Yes	No	No	No	HA, CHD

CNS, central nervous system; ANA, anti-nuclear antibodies; HA, hypertension; CHD, coronary heart disease; DM, diabetes mellitus.

3.2. Characteristics of SLE patients with hearing loss

Pure-tone audiometry disclosed sensorineural hearing loss in 10 patients (28.6%) with SLE. All of them were women, aged from 46 to 71 years, the SLE duration ranged from 2 to 25 years and seven patients had also other cardiovascular and metabolic diseases (Table 3). In these patients high-frequency SNHL– 2000 Hz and above – was observed except for one patient with hearing loss involving mid-frequencies (Fig. 1). In the group of patients with hearing loss, five persons revealed bilaterally acoustic reflexes for all frequencies and three persons did not reveal them for any. Two patients did not have bilateral reflexes for 500, 2000 or 4000 Hz.

3.3. Audiological evaluation of SLE group with respect to duration of the disease

The mean values of the air-conduction hearing thresholds in group A were significantly better than in group B for 3000

and 4000 Hz ($p < 0.05$) and than in group C for the frequencies from 2000 to 8000 Hz (2 and 3 kHz, $p < 0.05$; 4 and 8 kHz, $p < 0.01$; 6 kHz $p < 0.001$) (Fig. 2). There were no significant differences between groups B and C. Significant positive correlation between values of the mean air-conduction hearing thresholds and SLE duration ($r = 0.36$, $p < 0.001$) as well as with age ($r = 0.63$, $p < 0.005$) was found.

Because age can influence the results, to achieve more reliable hearing assessment depending on SLE duration, patients in each of A, B and C groups were divided into two subgroups: younger (up to 49 years old, $n = 19$ patients) and older (50 years old and above, $n = 16$ patients). Cardiovascular and metabolic diseases were more frequent in the older than in the younger patients (11/16 vs. 3/19, respectively). It was found that only in the first group there was a statistically significant association between hearing loss and disease duration. Among younger patients, those with short period of disease (group A) had better mean values of the air-

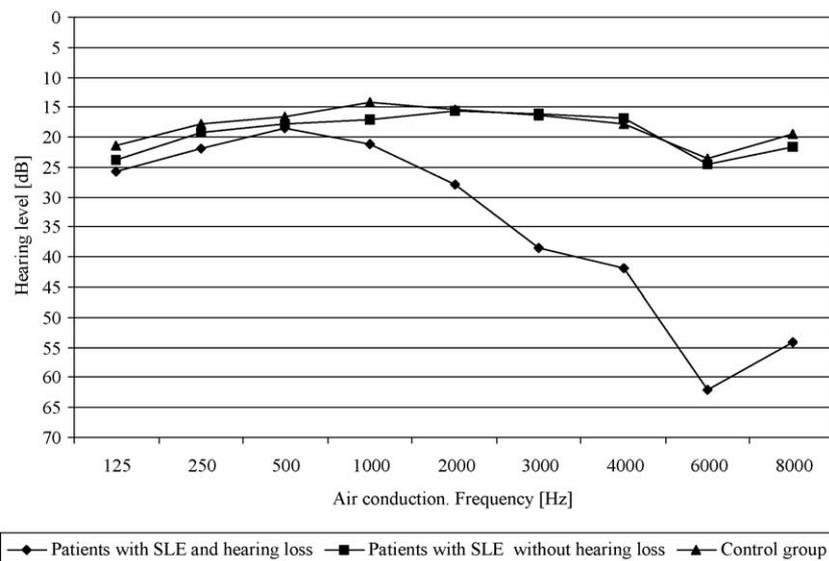


Fig. 1. Mean pure-tone audiogram of patients with SLE and hearing loss ($n = 20$ ears) compared to patients with SLE without hearing loss ($n = 50$ ears) and control group ($n = 60$ ears).

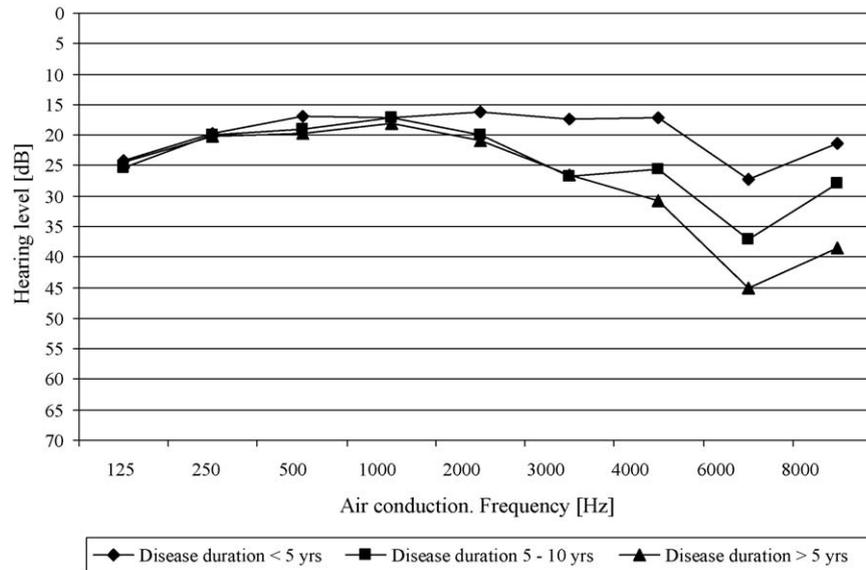


Fig. 2. Average audiograms of SLE patients related to disease duration ($n = 70$ ears).

conduction hearing thresholds compared to subjects affected by SLE for a long period of time (group C) for frequencies 2000, 4000, 6000 and 8000 Hz (13.9 dB vs. 22.5 dB, $p < 0.005$; 14.0 dB vs. 20.8 dB, $p < 0.05$; 22.3 dB vs. 40.0 dB, $p < 0.001$; 16.5 dB vs. 35.8 dB, $p < 0.01$, respectively) and those from group B (suffering from SLE for 5–10 years) had better mean values for frequency 6000 Hz compared to group C (22.5 dB vs. 40.0 dB, $p < 0.01$). There was no such association in the group of older patients (data not shown).

In younger group the significant multiple correlation for all variables like duration of disease and age was found (multiple correlation coefficient $r = 0.78$, $p < 0.001$). The duration of disease had contributed more significantly (linear regression coefficient $\beta = 0.58 \pm 0.12$, $p < 0.001$) than age ($\beta = 0.32 \pm 0.12$, $p < 0.02$) to the final model. In older group no multiple correlation was shown ($r = 0.22$, $p = 0.49$).

3.4. Audiological evaluation of SLE group with respect to severity of the disease

There were no differences in pure-tone averages between the group with and without renal involvement. The mean values of the air-conduction hearing thresholds in SLE patients in groups CNS(+) and AB(+) were poorer than in groups CNS(–) and AB(–) for 3000–8000 Hz, although the differences were not statistically significant (data not shown). No correlation was found between the hearing level and renal and CNS involvement or presence of antibodies.

3.5. Audiological evaluation of SLE group with respect to clinical features of the disease

The logistic regression analysis showed that in the SLE group hearing loss was related significantly only to the

cardiovascular diseases (regression coefficient $\beta = 2.72 \pm 1.11$, $p = 0.014$) and did not depend on clinical features of patients such as CNS ($p = 0.46$) and kidney involvement ($p = 0.16$), chloroquine diphosphate ($p = 0.59$) and corticosteroid therapy ($p = 0.21$) and the presence of antibodies associated with unfavourable SLE prognosis ($p = 0.97$).

4. Discussion

In the present study it was found that patients with systemic lupus erythematosus had poorer hearing thresholds than the age-matched controls. Sensorineural hearing loss was observed in 28.6% of patients, it was mainly bilateral, symmetrical and affecting high frequencies. There were no cases of fluctuating hearing loss. This was frequently not typical of autoimmune hearing loss as it is often regarded as bilateral, but asymmetrical, fluctuant and concerning initially mid-frequency range [5]. High-frequency hearing loss is often attributed to tonotopic base to apex differences in cochlea like viability of outer hair cells [16], vascularization [17], intrinsic susceptibility of basal hair cells to free radicals [18], which make a basal turn receptor more sensitive to damage [19]. Vasculitis processes, excessive generating of free radicals and the cochlear pathology in the stria vascularis observed in SLE animal model (MRL-Fas^{lpr} mouse) [20] seem to dominate in lupus pathology and hearing loss development in the course of the disease. In previous studies, ear involvement in patients with SLE was reported in 8–58.1% of the examined subjects [10,11,21–25]. Roverano et al. [19] observed asymptomatic sensorineural hearing loss at high frequencies in 66% of patients with SLE. In our patients there was also such difference between subjective and objective assessment of hearing loss because we noted four asymptomatic cases of hearing loss.

Interestingly, over 70% of SLE patients reported vertigo and dizziness in the questionnaire, so we plan further study to shed light on this issue. The prevalence of vertigo and/or balance disorders reported by SLE patients varies between 13% and 67% according to literature [10,11,23]. The balance system disorders may result from such factors as the presence of psychoneurological symptoms which are very frequent in SLE and concern about 77–80% of patients [26], cerebral blood flow impairment seen in imaging [27] and histopathological studies [28], the presence of antibodies to CNS elements [29] and also abnormalities observed in immunohistological studies of vestibular organ [30].

Hearing loss in systemic lupus erythematosus may be potentially due to autoimmunity, vasculitis, premature presbycusis and drug ototoxicity, as it was suggested by several authors [22,23]. All these factors may be more pronounced in long-lasting and exacerbated disease, so we tried to find out if hearing disorders were related to the course of SLE. In the present investigation we observed a relationship between SLE duration and the degree of hearing loss only in the group of patients up to 49 years old and not in the older one. This result can indicate that the SLE influence on hearing is seen mostly in younger patients and the other factors like process of ageing or medication may have an additional cumulative effect on hearing acuity in older patients. Moreover, older patients suffered much more often than younger ones from other cardiovascular diseases which might also cause hearing loss. These diseases were the only clinical factor which significantly contributed to hearing loss.

In our study we did not demonstrate any significant relationship between hearing threshold and severity of systemic lupus erythematosus. Our results are in agreement with other investigations which have not revealed possible correlation between age, organ-system involvement, SLE duration and severity [11,21,22,24,25]. Sperling et al. [23] observed that aural symptoms, like hearing loss and tinnitus, were more frequent in those SLE patients who had higher creatinine and lower C3 levels. A particularly interesting study of SLE patients was carried out by Bowman et al. [25]. All their patients were examined during hospitalisation because of aggravation of SLE, but the hearing loss was found only in 8% of the group. Our patients were examined during periods of remission, but, in spite of that, the presence of hearing loss was more frequent. The assessment of auto-antibodies is an acknowledged method of SLE diagnosis. Some of these antibodies have been linked to disease activity. But no work reporting a statistically significant increase in the incidence of antibodies and ear involvement could be located in the accessible literature [21,31]. Besides, in our study we did not find any correlation between the presence of antibodies corresponding with unfavourable prognosis in SLE and hearing loss. Only one out of 10 SLE patients with hearing loss had abnormally high titre of anti-nuclear antibodies.

Cases of sudden sensorineural hearing loss as a first manifestation of SLE or during exacerbation of the disease have been reported in the literature [25,32–34]. We observed also a similar case of sudden, profound, bilateral hearing loss, associated with anti-phospholipid syndrome, in our patient with coexistent lupus anticoagulant and viral infection [35]. Interestingly, the high doses of corticosteroids which were given to this patient due to aggravation of SLE, recommended also in the treatment of sudden deafness, did not improve hearing [36].

Localization of hearing loss in SLE is known as cochlear lesion but other sites may be also involved. In the current study increase of neural conduction was observed in SLE patients compared with controls, which can suggest subclinical retrocochlear or central involvement of the auditory pathway. Fradis et al. [37] have suggested that auditory brainstem response audiometry with high stimulation rate is a sensitive indicator of CNS subclinical disorders associated with systemic lupus erythematosus. This was not confirmed by Borton et al. [38]. Also in other studies, no abnormalities in conventional ABR or in middle and long latency auditory potentials were demonstrated [10,39]. However, our findings may be due also to prolonged use of chloroquine diphosphate, which is in line with the adverse effect of that drug on hearing reported by Bernard [40]. In patients subjected to chronic pharmacological therapy it would be not reasonable to exclude its participation in the etiology of hearing loss. Chloroquine diphosphate is one of the basic drugs used in SLE treatment and there are reports of its ototoxicity [41]. In the presented study, only two patients with hearing loss were not treated with chloroquine diphosphate.

The results of our study show that otologic symptoms are prevalent among patients with SLE and auditory system involvement should be taken into consideration during diagnostic and therapeutic procedures. However, the evaluation of its character, original or secondary, requires further research.

Acknowledgements

Granted by Medical university of Lodz, No 503-2036-1, 503-1036-3, 503-1152-2.

References

- [1] Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. *Dermatology*. Berlin/Heidelberg/New York: Springer; 2000.
- [2] Steinberg AD, Gourley MF, Klinman DM, Tsokos GC, Scott DE, Krieg AM. In: NIH conference. Systemic lupus erythematosus. *Ann Intern Med* 1991;115:548–59.
- [3] Schroeder JO, Euler HH. Recognition and management of systemic lupus erythematosus. *Drugs* 1997;54:422–34.
- [4] Suzuki N, Mihara S, Sakane T. Development of pathogenic anti-DNA antibodies in patients with systemic lupus erythematosus. *FASEB J* 1997;11:1033–8.

- [5] Ruckenstein MJ. Autoimmune inner ear disease. *Curr Opin Otolaryngol Head Neck Surg* 2004;12:426–30.
- [6] Mathews J, Rao S, Kumar BN. Autoimmune sensorineural hearing loss: is it still a clinical diagnosis? *J Laryngol Otol* 2003;117:212–4.
- [7] Amor-Dorado J, Arias-Nuñez MC, Miranda-Filloo JA, Gonzalez-Juanatey C, Llorca J, Gonzalez-Gay MA. Audiovestibular manifestations in patients with limited systemic sclerosis and centromere protein-B (CENP-B) antibodies. *Medicine* 2008;87:131–41.
- [8] Kastanioudakis I, Skevas A, Danielidis V, Tsiakou E, Drosos AA, Moustopoulos MH. Inner ear involvement in rheumatoid arthritis: a prospective clinical study. *J Laryngol Otol* 1995;109:713–8.
- [9] Alatas N, Yazgan P, Oztürk A, San I, Iynen I. Audiological findings in patients with ankylosing spondylitis. *J Laryngol Otol* 2005;119:534–9.
- [10] Skrzypczak W, Czuszyńska K, Narożny W, Siebiert J, Stankiewicz C, Kuczkowski J. Hearing evaluation in patients with Sjögren syndrome and systemic lupus erythematosus. *Otornolaryngologia-przegląd kliniczny* 2006;5:179–83.
- [11] Karatas E, Onat AM, Durucu C, Baglam T, Kanlikama M, Altunoren O, et al. Audiovestibular disturbance in patients with systemic lupus erythematosus. *Otolaryngol Head Neck Surg* 2007;136:82–6.
- [12] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of the systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- [13] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725–34.
- [14] Spoor A. Presbycusis values in relation to noise-induced hearing loss. *Int Audiol* 1967;6:48–57.
- [15] Gierek T. Assessment of perception ability of the hearing organ in the 250 to 20,000 Hz range during the aging process of the human organism. *Otolaryngol Pol* 1979;33:95–104.
- [16] Zajic G, Schacht J. Comparison of isolated outer hair cells from five mammalian species. *Hear Res* 1987;26:249–56.
- [17] Axelsson A, Ryan AF. Circulation of the inner ear, I. Comparative study of the vascular anatomy in the mammalian cochlea. In: Jahn AF, Santos-Sacchi J, editors. *Physiology of the ear*. 2nd ed., San Diego: Singular Publishing Group; 2001. p. 301–20.
- [18] Sha SH, Taylor R, Forge A, Schacht J. Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. *Hear Res* 2001;155:1–8.
- [19] Roverano S, Cassano G, Paira S, Chiavarini J, Graf C, Rico L, et al. Asymptomatic sensorineural hearing loss in patients with systemic lupus erythematosus. *J Clin Rheumatol* 2006;12:217–20.
- [20] Ruckenstein MJ, Keithley EM, Bennet T, Powell HC, Baird S, Harris JP. Ultrastructural pathology in the stria vascularis of the MRL-Fas/lpr mouse. *Hear Res* 1999;131:22–8.
- [21] Gomides AP, do Rosário EJ, Borges HM, Gomides HHM, de Pádua PM, Sampaio-Barros PD. Sensorineural dysacusis in patients with lupus erythematosus. *Lupus* 2007;16:987–90.
- [22] Andonopoulos A, Naxakis S, Goumas P, Lygatsikas C. Sensorineural hearing disorders in systemic lupus erythematosus. A controlled study. *Clin Exp Rheumatol* 1995;13:137–41.
- [23] Sperling N, Tehrani K, Liebling A, Ginzler E. Aural symptoms and hearing loss in patients with lupus. *Otolaryngol Head Neck Surg* 1998;118:762–5.
- [24] Kastanioudakis I, Ziavra N, Voulgari PV, Exarchakos G, Skevas A, Drosos AA. Ear involvement in systemic lupus erythematosus patients: a comparative study. *J Laryngol Otol* 2002;116:103–7.
- [25] Bowman C, Linthicum F, Nelson RA, Milkami K, Quismorio F. Sensorineural hearing loss associated with systemic lupus erythematosus. *Otolaryngol Head Neck Surg* 1986;94:197–204.
- [26] Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stalworth CL, et al. Neuropsychiatric syndromes in lupus. Prevalence using standardized definitions. *Neurology* 2002;58:1214–20.
- [27] Sibbit WL, Sibbit RR, Brooks WM. Neuroimaging in neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 1999;42:2026–38.
- [28] Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955–1977. *Semin Arthritis Rheum* 1979;8:212–21.
- [29] Kurki P, Helve T, Dahl D, Virtanen I. Neurofilament antibodies in systemic lupus erythematosus. *J Rheumatol* 1986;13:69–73.
- [30] Fukushima N, Fukushima H, Cureoglu S, Schachern PA, Paparella MM. Hearing loss associated with systemic lupus erythematosus: temporal bone histopathology. *Otol Neurotol* 2005;27:127–8.
- [31] Yee CS, Hussein H, Skan J, Bowman S, Situnayake D, Gordon C. Association of damage with autoantibody profile, age, race, sex and disease duration in systemic lupus erythematosus. *Rheumatology* 2003;42:276–9.
- [32] 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.
- [33] Green L, Miller E. Sudden sensorineural hearing loss as a first manifestation of systemic lupus erythematosus: association with anti-cardiolipin antibodies. *Clin Rheumatol* 2001;20:220–2.
- [34] 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;114:214–8.
- [35] Pajor A, Waszczykowska E, Erkiert-Polguj A, Maciaszczyk K. Bilateral sudden deafness in patient with systemic lupus erythematosus. *Post Dermatol Alergol* 2009;26:98–103.
- [36] Narożny W, Sicko Z, Przewoźny T, Stankiewicz C, Kot J, Kuczkowski J. Usefulness of high doses of glucocorticoids and hyperbaric oxygen therapy in sudden sensorineural hearing loss treatment. *Otol Neurotol* 2004;25:916–23.
- [37] Fradis M, Podoshin L, Ben-David J, Slatter P, Pratt H, Nahir M. Brainstem auditory evoked potentials with increased stimulus rate in patients suffering from systemic lupus erythematosus. *Laryngoscope* 1989;99:325–9.
- [38] Borton TE, Eby TL, Ball EV, Nolen BL, Bradley BL. Stimulus repetition rate on the auditory brainstem response in systemic lupus erythematosus. *Laryngoscope* 1992;102:335–9.
- [39] da Mata Rezende Mdos S, Iório MC. A study of auditory evoked potentials in systemic lupus erythematosus patients. *Braz J Otorhinolaryngol* 2008;74:429–39.
- [40] Bernard P. Alteration of auditory evoked potentials during the course of chloroquine treatment. *Acta Otolaryngol (Stockholm)* 1985;99:387–92.
- [41] Bortoli R, Santiago M. Chloroquine ototoxicity. *Clin Rheumatol* 2007;26:1809–10.