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MAIN ARTICLE

Young systemic lupus erythematosus patients with no hearing involvement: 10-year follow up

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Abstract

Objective: To evaluate patients with systemic lupus erythematosus and normal hearing over 10 years, compared with healthy controls.

Methods: Thirty patients diagnosed with systemic lupus erythematosus were evaluated in a prospective, descriptive study. Eight patients fulfilled the inclusion criteria, i.e. normal otoscopy, normal hearing, normal imaging and disease duration of less than one year. Eleven healthy companions of ENT patients were recruited as controls.

Results: At study commencement, the mean patient age was 32.75 years (range, 15–49 years) and there were no statistically significant audiometric differences between patients and controls. No statistically significant audiometric changes were found either within or between the patient and control groups at 10-year follow up.

Conclusion: These results supply no evidence for progressive hearing loss in systemic lupus erythematosus patients with no hearing involvement at study commencement. Therefore, we recommend audiometric tests only for systemic lupus erythematosus patients complaining of hearing loss, or for other clinical purposes. It is conceivable that asymptomatic hearing loss could be observed over a more extended follow-up period (i.e. more than 10 years).

Key words: Hearing Loss; Lupus Erythematosus, Systemic; Antibodies, Anticardiolipin; Antibodies, Antiphospholipid

Introduction

Systemic lupus erythematosus (SLE) has been described as a prototype immune complex disease with multiorganic effects due to the deposition of antibody–antigen immune complexes in the skin, joints, serous membranes, kidney, lung, brain and heart.

This disease has occasionally been associated with sudden, fluctuating or rapidly progressive forms of sensorineural hearing loss (SNHL).[1,2] Although symptomatic SNHL is rare in SLE, aural symptoms have been described with varying incidence (ranging from 0 to 57.5 per cent).[3] Since audiological disturbance in SLE could be more prevalent than previously recognised, audiological research should be directed toward routine, pure tone audiometry for patients with autoimmune disease.[4] Furthermore, the use of electronystagmography assessment for SLE patients with vestibular disturbance has also been suggested by Karatas *et al.*[5]

Although the pathogenesis of SNHL in patients with SLE is not clear, several reports have suggested an association with anticardiolipin antibodies[6] as well as antiphospholipid antibodies[7] through vascular damage within the inner ear.

We performed a prospective, 10-year, hearing evolution study in a cohort of young SLE patients with no initial hearing loss. The aim of this study was to determine the occurrence of subclinical SNHL and its possible progression over time.

Patients and methods

Thirty patients diagnosed in 1998 with SLE, and with less than one year's disease development, were studied at the otorhinolaryngology department of the Hospital Universitario Puerta de Hierro-Majadahonda (Table I). Systemic lupus erythematosus had been diagnosed following the American College of Rheumatology criteria.[8]

Exclusion criteria included a past history of audiovestibular disturbance, hearing loss, cranial trauma, acoustic trauma, abnormal magnetic resonance imaging of the inner ear, other otological diseases,

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TABLE I
PATIENT CHARACTERISTICS

Parameter	Value
Total patients (*n*)	30
Total loss to study (*n*)	22
Total patients in study (*n*)	8
Gender (F:M; *n*)	8:0
Age (mean (range); yr)	
– Study start	32.75 (15–49)
– Study end	43.00 (26–59)
Race (pts; *n*)	
– Caucasian	7
– Moroccan	1
Disease durn (mean (range); yr)	
– Study start	0.40 (0–1)
– Study end	10.5 (10–11)
Systemic effects (*n* (%))	
– Skin	6 (75)
– Joints	5 (62.5)
– Pleura	2 (25)
– Pericardium	3 (37.5)
– Kidney	3 (37.5)
– Liver	0
– Haematological disease	4 (50)
Current Rx (*n* (%))	
– Corticosteroids	3 (37.5)
– Anti-malarials	4 (50)
– Cyclophosphamide	2 (25)
– Methotrexate	0
– Azathioprine	1 (12.5)
– Mycophenolate	1 (12.5)
– Salicylates	5 (62.5)
– Cyclosporin A	1 (12.5)
AutoAbs present (*n* (%))	
– ANA	7 (87.5)
– Anti-DNA	6 (75)
– Anticardiolipin	2 (25)
– Antiphospholipid	3 (37.5)
– Lupus anti-coagulant	4 (50)

F = females; M = males; yr = years; pts = patients; durn = duration; Rx = medication; AutoAbs = autoantibodies

congenital hearing loss, or a family or genetic history of SNHL. These exclusion criteria were strictly applied to ensure that any SNHL which developed was potentially due to SLE.

Eleven healthy Caucasians who accompanied the ENT patients (nine women and two men of a similar age) were chosen as controls.

Clinical evaluation included a detailed history, physical examination and pure tone audiometry (using an Interacoustics AC 40 clinical audiometer; Assens, Denmark). Magnetic resonance imaging was performed in patients solely to exclude inner ear neoplastic pathology and malformations. All patients and controls were evaluated by standard pure tone audiometry (assessing air conduction thresholds at octave frequencies from 125 to 8000 Hz, and bone conduction thresholds at octave frequencies from 250 to 4000 Hz) less than 1 month after the diagnosis of SLE was established, and again after 10 years. Pure tone audiometry was repeated every year during the 10-year follow-up period (data not shown). Only the initial and final audiograms were included in the statistical analysis.

Hearing was considered to be normal when the pure tone average (i.e. the average of pure tone hearing thresholds at 500, 1000 and 2000 Hz) was less than 25 dB HL. A difference of at least 15 dB for a single frequency was required to consider a hearing threshold difference between the initial and final audiometry tests to be statistically significant.

The investigational protocol was approved by the local ethics committee. Written, informed consent was obtained from patients and controls.

In the statistical analysis, the Mann–Whitney U test for independent data was used to compare groups. Differences between initial and final values were analysed using the non-parametric Wilcoxon test for paired data. All data were analysed using SPSS (version 14.0) software for Windows (IBM, Armonk, New York, USA). Differences were considered statistically significant if the p value was less than 0.05.

Results

The present study included 8 women with an initial mean age of 32.75 years (range, 15 to 49 years). The mean duration of disease was 4.87 months. Corticosteroids (37.5 per cent), anti-malarials (50 per cent) and salicylates (62.5 per cent) were the most frequently prescribed medications. Anticardiolipin and antiphospholipid antibodies were observed in two and three patients, respectively.

The mean age of the control group at the beginning of the study was 34.36 years (range, 17 to 51 years). No otological symptoms (i.e. hearing loss, vertigo or tinnitus) were observed in this group.

The mean audiological results were within normal ranges at all frequencies (Figure 1). No patient had any history of sudden hearing loss. Tinnitus was present in only one case and remained unchanged throughout the study. Vertigo was observed at the first evaluation in two patients; however, this symptom disappeared during follow up. There were no differences between the initial values of the patient versus control groups, with respect to age or hearing threshold at any audiogram frequency.

There was no significant difference between the left and right ear dB HL hearing thresholds in either the study or control groups; therefore, all further analysis was carried out without reference to the side.

Comparison between initial and final audiological assessments showed no statistically significant changes after long-term follow up, in either the study or the control group (Table II). It is noteworthy that hearing thresholds at the majority of frequencies remained stable, with only the higher frequencies having more variable values; however, this variation was not considered statistically significant (Figure 1).

When final hearing threshold values were compared, there was no statistically significant difference between the two groups at any frequency.

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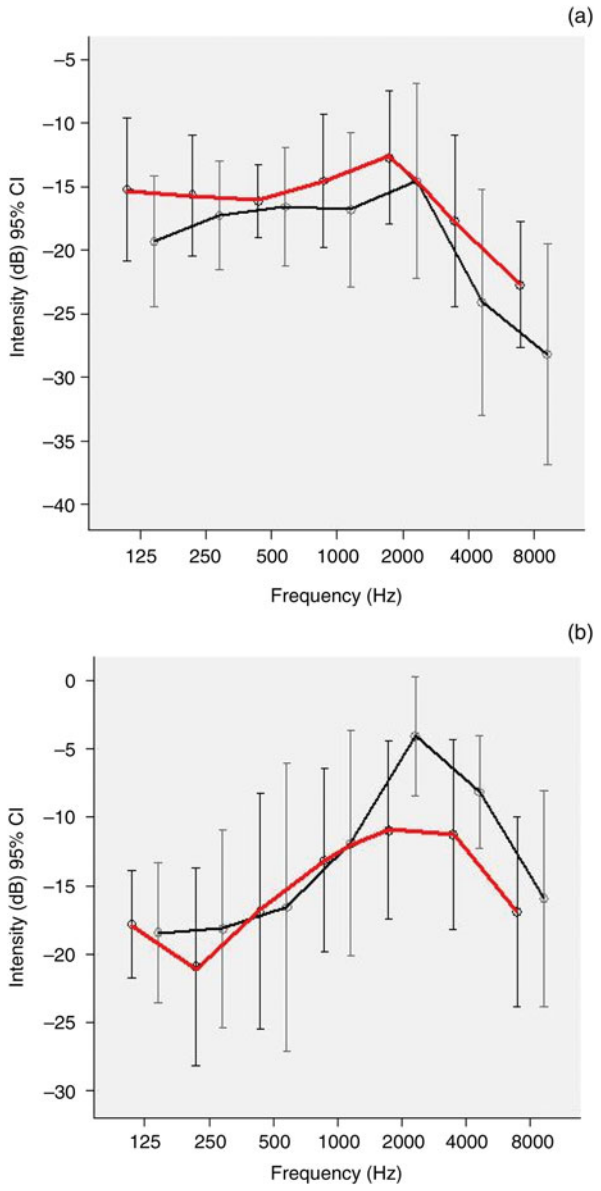

FIG. 1

Mean audiogram for (a) controls and (b) systemic lupus erythematosus patients, showing both ears, at the start (red line) and end (black line) of the study. CI = confidence interval

Discussion

The first report of autoimmune hearing loss was published in 1979 by McCabe.[9] Since then, numerous authors have described the presence of SNHL in several autoimmune disorders, although prevalence and frequency have varied between studies.[2,10]

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterised by the presence of autoantibodies and circulating immune complexes. Sensorineural hearing loss has been reported in SLE patients, and sudden hearing loss can be the initial symptom of the disease.[2] This form of presentation is one of the clinical manifestations of so-called immune-mediated inner ear disease.[11,12]

There have been many controversies regarding the existence of hearing loss in SLE patients. Andonopoulos *et al.*[13] found that a significant number of clinically asymptomatic patients with the disease had subclinical sensorineural hearing abnormalities, especially at low frequencies. This could suggest endolymphatic hydrops, but temporal bone studies have only occasionally shown this pathological finding.[14] Recently, Karabulut *et al.*[15] reported a general picture of low frequency hearing loss in SLE patients, and considered these results to be related to endolymphatic and cochlear hydrops. However, an increased prevalence of subclinical or slowly progressive SNHL has been reported in SLE patients.[16–18] Based on their audiometric studies, Roverano *et al.*[4] have recommended that audiometric tests be included as part of initial studies in patients with systemic lupus disease.

Based upon our results, we were unable to prove the existence of progressive hearing loss in a subset of young patients in whom SLE had developed for less than one year; these patients did not demonstrate any difference from a healthy control group with respect to pure tone audiometry. In contrast, a study by Maciaszczyk *et al.*[18] found that SLE patients had poorer hearing thresholds than controls. It is possible that immunosuppressive therapy could mask or inhibit the immune mechanisms that lead to SNHL. In the present study, no correlation was found between SLE duration and age or hearing loss. This was possibly due to the younger age of our patients (mean age, 32.75 years) and their short mean duration of disease (less than 1 year in all; mean duration, 4.87 months). However, Maciaszczyk *et al.*[18] have suggested that, over a longer period, SLE may lead to SNHL.

The cause of inner ear injury in SLE is not well known. Caldarelli *et al.*[2] suggested vasculitis and microinfarctions caused by the deposition of immune complexes in the temporal bone microvessels (capillaries and arterioles).[2] Sone *et al.*[14] showed a loss of spiral ganglion and hair cells as well as atrophy of the stria vascularis. Bouman *et al.*[19] demonstrated that endolymphatic hydrops was caused by perisaccular deposition of immune complexes. The present study excluded patients affected by hearing disturbance, who could have shown such aetiologies (data not published).

Some potentially ototoxic drugs used in autoimmune disorders, such as hydroxychloroquine and furosemide, could play a role in some cases of irreversible and reversible SNHL observed in such patients.[20] Nevertheless, Compadretti *et al.*[7] reported the case of a patient who received hydroxychloroquine therapy for three years but did not show any signs of cochlear damage.

The association with anticardiolipin antibodies[6] and antiphospholipid syndrome[7] supports the theory that autoimmune-associated SNHL is caused by a thrombotic mechanism. This theory was first postulated by Hisashi *et al.*[6] to explain the fact that SLE patients

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TABLE II
HEARING THRESHOLDS

Freq (Hz)	Time point	Control group (dB)*					SLE group (dB)†				
		Mean ± SD	Range	Percentiles			Mean ± SD	Range	Percentiles		
				25th	50th	75th			25th	50th	75th
Right ear											
125	Start	13.6 ± 7.4	5–25	5	10	20	2.00 ± 5.3	15–30	15	20	23.7
	End	19.5 ± 8.2	5–35	15	20	25	20.0 ± 6.5	10–30	15	20	25
250	Start	15.0 ± 5.4	5–20	10	15	20	23.7 ± 12.4	5–45	12.5	25	30
	End	17.7 ± 6.4	10–35	15	15	20	20.6 ± 11.7	5–40	11.2	17.5	30
500	Start	18.1 ± 6.0	10–30	15	20	20	20.0 ± 15.8	5–55	7.5	17.5	23.7
	End	18.1 ± 7.8	10–35	15	15	20	20.6 ± 16.5	10–55	10	10	30
1000	Start	14.0 ± 6.6	5–25	10	15	20	15.0 ± 10.0	5–35	6.2	12.5	20
	End	18.6 ± 8.6	5–35	10	20	25	15.0 ± 13.8	0–40	5	10	27.5
2000	Start	14.5 ± 9.0	5–30	5	10	25	11.2 ± 9.1	5–30	5	7.5	17.5
	End	16.8 ± 11.8	0–35	0	20	25	4.3 ± 4.9	0–15	0	5	5
4000	Start	19.0 ± 10.9	5–35	10	20	30	11.8 ± 10.6	0–30	1.2	10	20
	End	24.5 ± 16.0	0–55	15	20	35	8.7 ± 6.4	0–15	1.2	10	15
8000	Start	20.4 ± 6.1	10–30	15	20	25	21.5 ± 11.5	10–45	11.2	20	27.5
	End	29.0 ± 15.7	5–55	20	30	40	14.3 ± 10.5	5–30	5	12.5	23.7
Left ear											
125	Start	16.8 ± 10.5	0–40	10	15	20	15.6 ± 4.9	10–20	10	17.5	20
	End	19.0 ± 9.1	0–35	15	20	25	16.8 ± 6.5	5–25	15	15	23.7
250	Start	16.3 ± 10.5	0–40	10	15	20	18.1 ± 6.5	5–25	15	20	23.7
	End	16.8 ± 7.1	5–30	15	15	25	15.6 ± 7.7	5–30	10	15	20
500	Start	14.0 ± 7.3	0–30	10	15	15	13.7 ± 6.4	0–20	11.2	15	18.7
	End	15.0 ± 6.7	5–25	10	25	20	12.5 ± 8.8	5–30	5	10	18.7
1000	Start	15.0 ± 9.7	5–40	10	15	20	11.2 ± 6.9	0–20	6.2	10	18.7
	End	15.0 ± 10.9	5–45	10	15	15	8.7 ± 6.4	0–20	5	7.5	13.7
2000	Start	10.9 ± 7.3	0–25	5	10	15	10.6 ± 7.2	0–20	5	10	18.7
	End	12.2 ± 12.7	0–45	5	10	15	3.7 ± 6.4	−5 to 15	0	2.5	8.7
4000	Start	16.3 ± 10.5	5–40	5	15	20	10.6 ± 6.7	0–20	6.2	10	17.5
	End	23.6 ± 12.4	10–55	15	20	25	7.5 ± 5.9	0–15	1.2	7.5	13.7
8000	Start	25.0 ± 12.8	5–50	20	25	35	12.5 ± 9.2	0–30	6.2	10	18.7
	End	27.2 ± 11.2	5–50	20	25	35	17.5 ± 10.3	0–35	11.2	17.5	23.7

*$n = 8$; †$n = 11$. Freq = frequency; SLE = systemic lupus erythematosus; SD = standard deviation; Start = study of study; End = end of study

with antiphospholipid syndrome usually presented with sudden SNHL. The mainstay of antiphospholipid syndrome treatment is anticoagulation. In contrast, most SLE patients suffering from sudden SNHL are treated with corticosteroids. Although our patients did not present with hearing loss, none of those with hearing alterations (excluded from the present study) showed any sudden SNHL; however, this finding could be related to the low percentage of antiphospholipid antibodies observed.

In our series, no significant relationship was demonstrated between hearing threshold and SLE severity. This result agrees with those of other studies which found no correlation between hearing threshold and age, organ system involvement, SLE duration or SLE severity.[1,4,12,16,17,20] However, this may be due to the

TABLE III
SYSTEMIC LUPUS ERYTHEMATOSUS PATIENT CHARACTERISTICS: PREVIOUS DATA

Study	Pts (*n*)	Age (mean (range); yr)	SNHL (pts; %)	Therapy	Anticardiolipin Abs* (pts; %)
Bowman *et al.*[1]	30	32.4 (21–61)	8	Corticosteroids, diuretics, NSAIDS	NR
Kastanioudakis *et al.*[21]	43	47.86†	21.5	Steroids, hydroxychloroquine, nifedipine, azathioprine, cyclosporin A, NSAIDS, MTX	10.52
Cordeschi *et al.*[16]	30	41 (27–66)	NR	NSAIDS, MTX, DHEA, cyclophosphamide	20
Gomides *et al.*[17]	45	30.9 (18–59)	15.6	Corticosteroids, anti-malarials, cyclophosphamide, platelet anti-aggregation agent	20
Karatas *et al.*[5]	28	35.6 (18–71)	21.42	NR	32
Present	8	32.75 (15–49)	0	Corticosteroids, anti-malarials, cyclophosphamide, azathioprine, cyclosporin A, MTX, mycophenolate, salicylates	25

*Immunoglobulin G and M. †Standard deviation = 12.69. Pts = patients; yr = years; SNHL = sensorineural hearing loss; Abs = antibodies; NSAIDS = non-steroidal anti-inflammatory drugs; MTX = methotrexate; NR = not reported; DHEA = dehydroepiandrosterone

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small number of patients enrolled in our study; therefore, our findings must be interpreted with caution.

Cordeschi *et al.*[16] observed progressive cochlear impairment in SLE patients.

The majority of reports[5,13,15–17,21] compared patient hearing assessments with those of age-matched, healthy subjects. However, the present study utilised two types of comparison to assess the hearing of a group of young SLE patients: SLE patients versus healthy control subjects, and initial versus final hearing values after long-term follow up.

- **Systemic lupus erythematosus (SLE) has been termed a prototype immune complex disease**
- **Sensorineural hearing loss may occur in SLE, and may be its presenting symptom**
- **This 10-year follow-up study found no hearing loss in young SLE patients**
- **Young SLE patients need audiological investigation only for evident hearing loss or other clinical reasons**
- **Other hearing tests are time-consuming and not cost-effective**

Our study patients were enrolled at a younger age than those of previously reported studies; however, at 10-year follow up our patients' mean age was similar to that of patients reported earlier (Table III). Considering the age of our patients, it would be reasonable to exclude the effect of some inner ear disorders, such as age-related hearing loss (presbycusis) and long-term exposure to environmental noise (e.g. noise pollution).

Conclusion

Although hearing loss can be an epiphenomenon in the clinical course of SLE patients, our data do not confirm any deterioration in the hearing of a group of young SLE patients without initial hearing loss: regarding hearing loss, these patients behaved like our healthy control subjects. Nevertheless, further research including a larger number of patients would be required to confirm these findings.

We would recommend investigative audiological assessment only for those SLE patients who complain of hearing loss, or for other clinical purposes.

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