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Hearing Loss Evaluation of Sjögren's Syndrome Using Distortion Product Otoacoustic Emissions

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Sjögren's syndrome (SS) is a cell-mediated immune disorder primarily affecting the exocrine glands and hearing loss may be the first otological manifestation of this autoimmune disease. In order to assess the degree of sensorineural hearing loss in SS, 22 female patients were examined by means of standard audiometric tests (pure-tone audiometry, acoustic reflexes and impedance testing) and using distortion product otoacoustic emissions (DPOAEs). The results indicated that only 36.3% of the patients had mild sensorineural hearing loss. Hearing level and distortion product threshold estimates were found to be significantly correlated. No relationship was found between the duration of the disease and the DPOAE and hearing threshold variables. The data suggest that SS may not directly cause sensorineural hearing loss. *Key words*: *autoimmune disease*, *distortion product otoacoustic emissions*, *Sjögren's syndrome*.

INTRODUCTION

The hypothesis suggesting that some inner ear disorders may be caused by an autoimmune response is almost 70 years old (1). This hypothesis has been supported by recent clinical findings describing a group of ''autoimmune inner ear disorders'' (AIED). AIED are a heterogeneous group of diseases associated with an immunoreactivity to inner ear components. Recently, Boulassel et al. (2) have demonstrated that antibodies to myelin P0 and β-actin proteins are found in the serum of patients suffering from AIED; abnormal expression of these proteins may lead to a dysfunction of the cellular-signal transduction and consequently to various vestibulo-auditory complications.

Sjögren's syndrome (SS) is a cell-mediated immune disorder of unknown etiology, primarily affecting the exocrine glands. In a number of autoimmune diseases, such as Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and SS, hearing loss has been reported (3) to be the first otological manifestation of the disease. A recent study by Fox et al. (4) has confirmed that 500,000 to 2 million SS patients in the US have hearing loss. SS is more frequent in females (female:male ratio = 9 : 1) aged > 50 years and this could be related to the influence of sex hormones, as androgens play an immune suppressor role whilst estrogens act as immuno-stimulants.

The clinical manifestations of SS are ocular, oral and extraglandular, relating to keratoconjunctivitis sicca and salivary gland lymphocytic infiltration. The vasculitic lesions and systemic manifestations are related to the deposition of immune complexes (ICs), which are considered the main causes of the high prevalence of cranial neuropathy (2, 4, 5). A recent study by Ziavra et al. (6) reported that the pathogenetic autoantibodies seem to be associated with certain clinical aspects, such as the early onset of the disease, swelling of the salivary glands, the degree of lymphocytic infiltration, leucolymphopenia, hypergammaglobulinemia, lymphoadenopathies and the vasculitic manifestations. The site of ear damage was located in the cochlea, mainly affecting the high frequencies, and a statistically significant correlation between sensorineural hearing loss (SNHL) and the duration of the disease was found. It should be noted that in cases of SS the deposition of ICs in the stria vascularis or in the endolymphatic sac via complement activation is related to endolymphatic hydrops (1, 3, 7).

In order to evaluate the incidence of SNHL involved in SS we examined a number of SS patients using standard audiometric methods such as pure-tone audiometry (PTA), acoustic reflexes and impedance tympanometry. To evaluate the mechanisms of SNHL we examined the SS patients using distortion product otoacoustic emissions (DPOAEs). The involvement of the latter technology was considered advantageous because DPOAEs convey useful information about the status of the cochlear functionality (8–14) and have been used extensively in hearing research and clinical practice.

MATERIALS AND METHODS

Patients

Between February 2000 and June 2001, 22 female SS patients were referred to the Audiology Department of Ferrara University via a collaboration with the Department of Rheumatology. The average duration

of disease in these patients was ≈ 3 years. The patients were identified as SS cases based on criteria from a European consensus project (3). Figure 1 shows the distributions of the ages and disease durations of the patients included in the study.

Inclusion criteria for the study were an intact tympanic membrane, no previous use of ototoxic drugs such as Plaquenil (hydroxychloroquine sulfate) and no history of otorrhea, otologic surgery, exposure to occupational or recreational noise, skull trauma or infection of the upper respiratory tract for at least 1 month before the beginning of the study. None of the patients presented with a history of concomitant tinnitus or vertigo.

Battery of tests

All patients underwent a battery of immunological tests, including those for rheumatoid factor, antinuclear antibodies, anti-Ro(SSA) and anti-La(SSB) autoantibodies, nuclear antigens, anticardiolipin antibodies and anti-neutrophil cytoplasmic antibodies.

The auditory function of each subject was assessed by means of a clinical examination involving anamnesis and audiometric tests, including PTA, tympanometry, stapedial reflexes and reflex decay measurements. The volume of information obtained was necessary in order to exclude cases of conductive hearing loss. For the hearing threshold measurements each subject was tested with octave frequencies ranging from 0.5 to 8 kHz. The criteria of normality was a hearing level (HL) of ≤ 20 dB in the tested octave frequencies. For the acoustic reflex thresholds, the subjects were tested ipsilaterally and contralaterally with frequencies ranging from 0.5 to 4 kHz. The reflex decay measurement was performed contralaterally for the frequencies 0.5 and 1 kHz.

DPOAEs were recorded with the ILO-292 apparatus (Otodynamics Ltd) using software version 5.6. The responses were evoked by an asymmetric protocol with $L_1 = 75$ and $L_2 = 65$ dB sound pressure limit (SPL) and a noise level set at -10 dB. Prior to each recording an *in situ* calibration was conducted to test the fit and the ILO-292 probe and to ensure proper stimulation at the tested frequencies. The cubic-difference DPOAE responses ($2f_1 - f_2$) were tested at the following five frequencies (referenced to f_2): 1.0, 2.0, 3.0, 4.0 and 5.0 kHz. Higher frequencies were not tested because above 5 kHz the frequency response of the ILO-probe is not linear. Each response was optimized using an ILO macro as described previously (15, 16). The data were analyzed in terms of signal-to-noise (S/N) values at each tested frequency. In order to accept a DPOAE response as valid, a S/N ratio equal to 3 dB was established as the criterion of normality per tested frequency.

To evaluate the degree of hearing loss and the correlation between the DPOAE and the PTA threshold values, we used, for each patient, data from the ear with the lower hearing threshold. The level of significance in the correlation and ANOVA studies was defined as $p < 0.05$. For all statistical analyses SPSS version 8.0 was used.

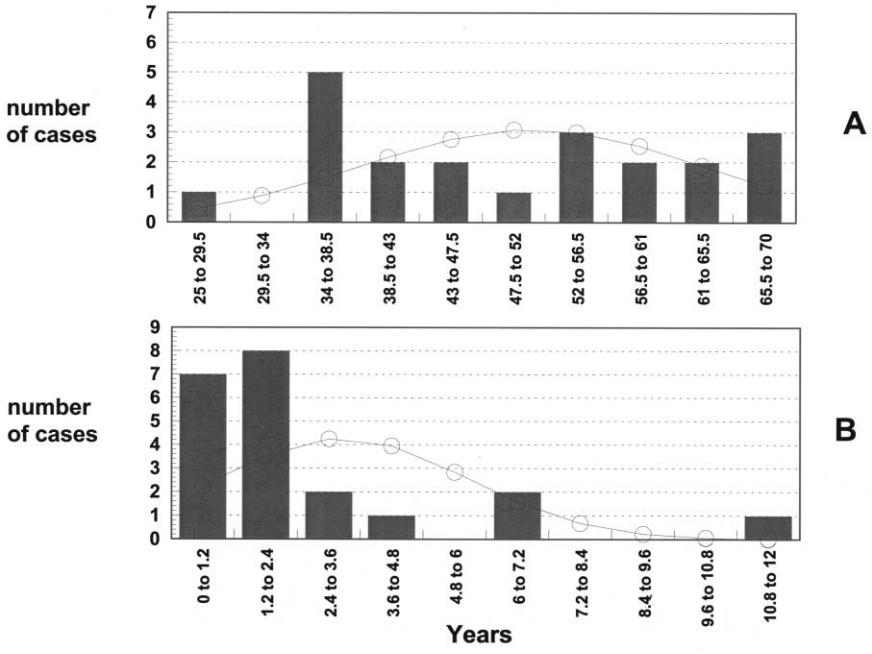

Fig. 1. Histograms showing (*A*) age distribution (mean 48 ± 12.5 years) and (*B*) distribution of duration of disease (mean 3 ± 2.8 years) for 22 female patients with SS. The overlaid curves represent the corresponding normal data distributions.

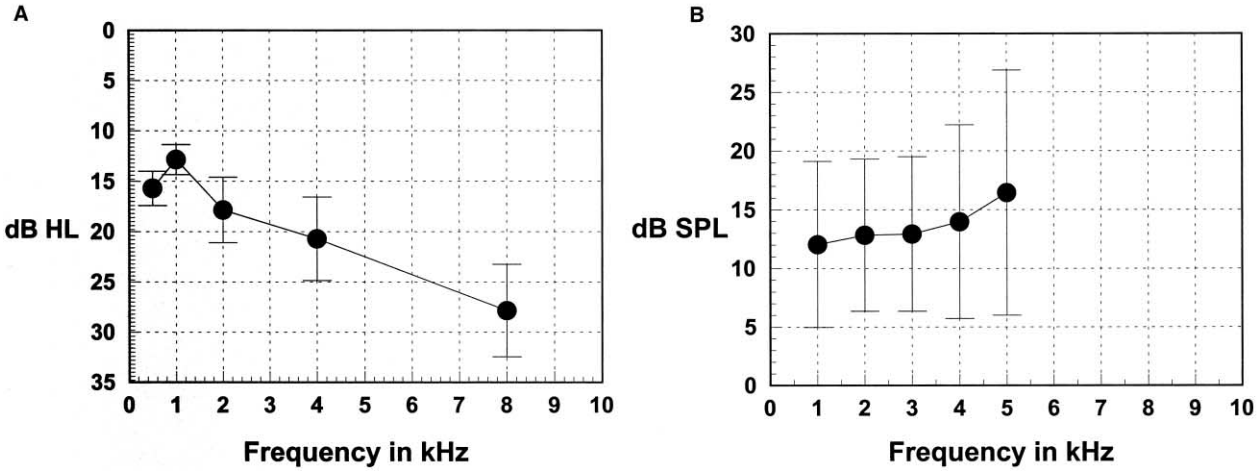

Fig. 2. (*A*) Mean threshold level values at the tested frequencies 0.5, 1.0, 2.0, 4.0 and 8.0 kHz and (*B*) mean S/N DPOAE values at the tested frequencies 1.0, 2.0, 3.0, 4.0 and 5.0 kHz (referenced to f2) for 22 female patients with SS. The error bars indicate one standard error of the mean.

Table I. *DPOAEs (dB) recorded from 22 female patients with SS*

Frequency (kHz)	Range	Minimum	Maximum	Mean	SD
1	23.50	1.00	24.50	12.03	7.00
2	18.10	3.40	21.50	12.82	6.50
3	24.10	1.70	25.80	12.92	6.58
4	23.70	3.70	26.40	13.96	8.25
5	22.60	3.30	25.90	13.45	7.12

RESULTS

The audiometric profiles of the SS patients are shown in Fig. 2*A*. All subjects presented normal tympanograms and the measurements of the acoustic reflex thresholds were within normal limits both contralaterally and ipsilaterally. Eight cases (36.3%) presented mild SNHL in the high frequencies (2.0 and 4.0 kHz), distributed evenly in the following 2 ranges: 4 in the range >20 and <30 dB HL and 4 in the range >30 and <40 dB HL. The term "threshold" in this context refers to the average hearing level at 2.0 and 4.0 kHz.

The DPOAE data are shown in Table I and Fig. 2*B*. For the majority of cases all S/N ratios were >3 dB, with the exception of two cases with low S/N ratios of 1.0 and 3.0 kHz, respectively. The largest DPOAE S/N ratios were observed at $f_2 = 4.0$ kHz. At this frequency the level of noise was significantly lower and thus the corresponding S/N ratio was maximized. As is common in recordings of DPOAE responses, the lowest S/N ratios were observed at $f_2 = 1.0$ kHz. Using a discriminant analysis procedure, based on an earlier study (17), the DPOAEs from the SS dataset were compared with normative and hearing loss adult data stored in the database of our laboratory. The results showed that the SS DPOAE responses could be classified as normal. In this context, it might be said that the SS patients were characterized by normal cochlear function.

Plots of the S/N ratios (DP-grams) at the tested frequencies are shown in Fig. 3. Several configuration patterns were observed, but the commonest showed either a descending (Fig. 3*A*) or ascending pattern (Fig. 3*B*).

The correlation between PTA thresholds and DPOAE S/N ratios is shown in Table II. The Spearman estimates obtained indicated that there was a good correlation (negative relationship) between the auditory threshold values and the DPOAE responses. The data also suggest that a given PTA frequency (1.0, 2.0 or 4.0 kHz) correlates not only with the corresponding DPOAE frequency but with adjacent DPOAE frequencies as well.

ANOVA analyses between the PTA variables (hearing thresholds at 1.0, 2.0 and 4.0 kHz), the DPOAE S/N ratios at 1.0, 2.0, 3.0, 4.0 and 5.0 kHz, the patient's age and the duration of disease resulted in no significant relationships.

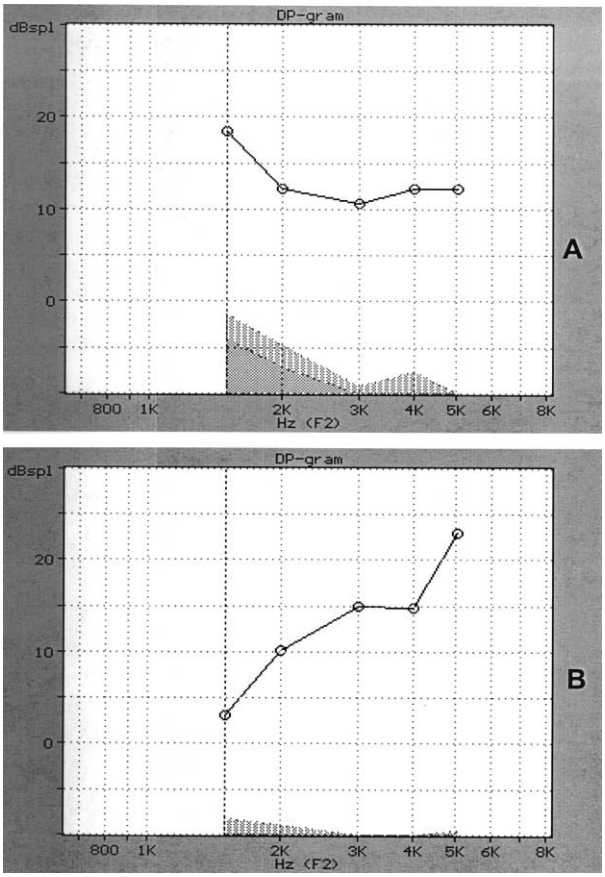

Fig. 3. The 2 dominant DP-gram patterns observed in the responses from 22 female patients with SS: (*A*) typical ascending pattern; (*B*) typical descending pattern. In both panels, the y-axis is the DPOAE amplitude and the x-axis is the tested DPOAE frequency referenced to f2. The shaded areas represent estimates of the level of noise in the DPOAE response.

DISCUSSION

Although hearing loss has been previously documented in patients with SS, the effect of SS on hearing is not well defined. Previous studies relating hearing loss to SS have reported a wide range of incidence of SNHL. The earliest study of SS patients by Dolg et al. (18) reported only 1 case (4.5%) with SNHL in a population of 22 patients. Ziavra et al. (6) evaluated 45 patients and reported SNHL losses in 22.5%. Trott et al. (19) evaluated 14 patients and reported SNHL losses in only 3 cases (21.4%). Tumiati et al. (5) evaluated a group of 30 patients and reported hearing losses in 46%. The results of our study, reporting a 36.3% incidence of SNHL, are in accordance with these previous studies.

In order to increase our knowledge of hearing loss relating to SS we examined our patients using a DPOAE protocol. A significant (negative) relationship was found between the DPOAE S/N ratios and the PTA threshold levels at the corresponding frequencies. These data verify the results of previous studies (20, 21) stating that when middle ear status is normal the PTA and DPOAE data are in agreement. The observed SNHL losses were classified as mild by PTA standards, but the results of the DPOAE discriminant analysis suggested that the actual hearing losses may have been less pronounced than indicated by the PTA data.

Despite the fact that the DPOAE responses from the SS patients were categorized as normal, for a number of DPOAE recordings a DP-gram notch was observed. Typical examples of this behavior are shown in Fig. 4. These DP-gram notches have been observed previously in adult and neonatal ears (16) and it is postulated that they represent a constructive interaction between a standing wave in the external meatus and the cochlear $2f_1-f_2$ DPOAE response. Re-inserting the ILO probe in a slightly deeper position in the meatus usually minimizes this effect.

Table II. *Correlation between the hearing threshold levels (dB HL) and the DPOAE responses (dB SPL) at 1.0, 2.0 and 4.0 kHz from 22 female patients with SS. The Spearman correlation estimates are shown, together with the probability that the correlation estimate is significant*

DPOAE response	Hearing threshold level						
	1 kHz	2 kHz	4 kHz	DP–1.0 kHz	DP–2.0 kHz	DP–3.0 kHz	DP–4.0 kHz
1 kHz	1	0.908**	0.689**	−0.573**	−0.655**	−0.402	−0.587**
		0	0	0.004	0.001	0.057	0.003
2 kHz	0.908**	1	0.616**	−0.486*	−0.568**	−0.437*	−0.562**
	0		0.002	0.019	0.005	0.037	0.005
4 kHz	0.689**	0.616**	1	−0.425*	−0.620**	−0.483*	−0.538**
	0	0.002		0.043	0.002	0.02	0.008

* Correlation is significant at the 0.05 level (two-tailed).
** Correlation is significant at the 0.01 level (two-tailed).

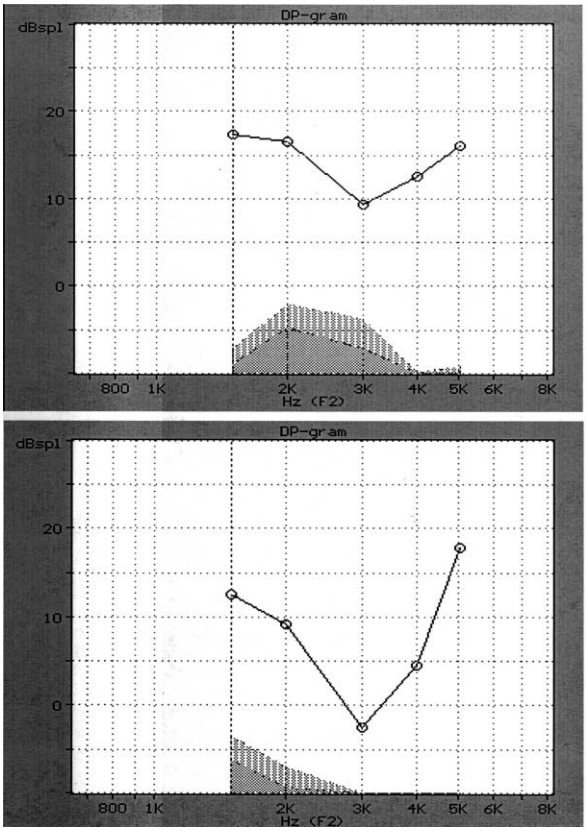

Fig. 4. Two examples of typical notches in the DP-grams of the tested subjects with SS. The DP-gram notch always occurred at the tested frequency 3.0 kHz (referenced to f2). In both panels, the y-axis is the DPOAE amplitude and the x-axis is the tested frequency referenced to f2. The shaded areas represent estimates of the level of noise in the DPOAE response.

No significant relationship was found between the duration of SS and the corresponding hearing threshold data and DPOAE S/N values. These findings contrast with the data reported by Ziavra et al. (6), whose study concluded that SNHL was associated with the duration of disease. The difference between the two studies may have been caused by the different mean disease durations. In the present study the SS duration was estimated as 3 ± 2.8 years, as opposed to 8.3 ± 5.4 years in the study of Ziavra et al.

This study show that only a small percentage of SS patients are affected by mild SNHL. The fact that the duration of SS was not significantly correlated with the PTA or DPOAE values and the wide range of SNHL incidence in tested patients, as reported in the literature, may suggest that SS may not directly cause SNHL, either immunomediated or otherwise.

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