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ORIGINAL ARTICLE

Evaluation of hearing and cochlear function by DPOAE and audiometric tests in patients with ankylosing spondilitis

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Abstract The aim of this study was to investigate cochlear functions in patients with ankylosing spondilitis (AS). Prospective, case control study. Twenty-eight AS patients (56 ears) and 25 healthy control subjects (50 ears) were included in the study. Pure-tone audiometry at 250, 500, 1,000, 2,000, 4,000, 6,000 Hz and immittance measures including tympanometry and acoustic reflex and DPOAEs (Distortion Product Otoacoustic Emission) testing were performed in the patients and controls. Pure-tone audiometry findings of the patients and controls were significantly different in all frequencies ($P < 0.05$). Sensorineural hearing loss was found in 10 patients (35%) that was bilateral in seven and unilateral in three patients. On DPOAE testing, there was no statistically significant difference between the levels of noise floor of the patients and controls ($P > 0.05$). However, the DPOAE responses of the patients and controls were significantly different in 3,000, 4,000, 5,000 and 6,000 Hz frequencies ($P < 0.05$). There is a damage of outer hair cells in patients with AS, and damaged outer hair cell regions mostly corresponds to the basal and mid-portions of the cochlea.

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Introduction

Ankylosing spondilitis (AS) is a chronic systemic inflammatory rheumatic disorder of uncertain etiology that primarily affects spine and sacroiliac joints. The diagnosis of AS is based on clinical features, and clinical diagnosis is usually supported by radiologic evidence of sacroiliitis [1]. The disease usually starts in the third decade of life and affects men three times more often than women [2].

Many studies and reports have been published about hearing loss in rheumatoid arthritis in the literature. However studies about hearing loss in AS have been limited.

Three case reports about hearing loss in patients with AS were published until now. Hearing loss was conductive type in a report [3] and sensorineural type in two reports [4, 5]. In addition to these case reports, recently, a clinical study was published, in which the investigators found sensorineural hearing loss in 28.6% of the AS patients. Sensorineural hearing loss was bilateral in four patients and unilateral in four patients and was particularly in the high frequencies. Auditory brainstem responses showed no significant differences between patients and controls [6].

In our clinical practice we usually observe that sensorineural hearing loss is more frequent than conductive hearing loss in patients with AS. Therefore, this study performed to investigate cochlear functions in patients with AS.

Materials and methods

Patients

Totally, 28 AS patients (56 ears) who were diagnosed and treated in the Physical Medicine and Rehabilitation Clinic of Numune Research and Training Hospital and 25 healthy control subjects (50 ears) were included in the study. The diagnosis of AS was done according to the Modified New York Diagnostic criteria [7]. Informed consent was obtained from all participants. Detailed information was obtained about possible etiological factors leading to hearing loss (ototoxic drugs, noise exposure, ear surgery, perforated tympanic membrane, Meniere's disease, cranial trauma, metabolic diseases). There were no patients who have had a history of these factors.

Participants were excluded from the study if they had any of following: (1) otoscopic evidence of a perforated tympanic membrane or other middle ear pathology, (2) presence of a flat tympanogram or absence of acoustic reflexes at 1 kHz with contralateral stimulation, (3) an air-bone gap of ≥5 dB at any frequency. Thus, four patients (4 ears) were excluded from the study, because one patient had history of trauma, one had no DPOAE response and two had deformed ear canal leading to unfit of probe insertion. Any DPOAE response that patients have a sensorineural hearing loss more than 60 dB and overlapping with noise floor were excluded from the study.

Audiometry

The initial hearing examination included otoscopy, tympanogram and complete audiologic evaluation including pure-tone air- and bone-conduction audiometry and speech audiometry. Pure-tone audiometry was performed at the frequencies 250, 500, 1,000, 2,000, 4,000, 6,000 Hz using a AC-40 diagnostic audiometer in a sound-treated cabin (Interacoustic Company, Denmark). Normal middle ear function was defined by immitance and acoustic reflex results using a Interacoustic AZ 26 Clinical impedencemeter. The patients and controls who had had normal peak compliance, peak pressure, gradient, ear canal volume and acoustic reflexes obtained by immitance measures, as defined by American Speech Language and Hearing Association [8, 9] were included in the study.

DPOAE testing

Distortion Product Otoacoustic Emission (DPOAEs) were measured using a Otodynamics ILO 292 Echoport equipment (Otodynamics Ltd., London) with ILO-OAE software installed on the computer (1.5 GHz Pentium IV processor). Equilevel primary tones f_1 and f_2 were fixed at $f_1/f_2 = 1.22$, and f_2 frequencies ranged from 1,000 to 6,000 Hz in 1/3 octave steps. Stimulus intensities were $L_1 = L_2 = 70$ dB. The individuals were seated in a soundproof room to remain as quiet as possible during the test. Once the probe was placed with a good seal in the ear canal, the level of the two frequencies was set according to our protocol. Each test protocol session took as a minimum of 100 s.

The statistical analyses were performed using SPSS 13.0 for Windows. A P value of <0.05 was considered significant. For overall groups comparisons of the groups (patients with AS and controls) independent samples t test was performed. For the ages of patients and controls comparisons, *chi-square* test and for the genders of patients and controls comparisons, Mann–Whitney U test was used. Pearson correlation analysis was used to investigate relationship between the quantative variables.

Results

The mean age of patients with AS was 34.3 (range 23–60) years. Three were female and 25 were male patients. The mean age of control group was 28.4 (range 20–38) years, there were 8 female and 17 were male subjects. Otoscopic examination was normal in all patients participants. There was no statistically significant difference between the ages and genders of the patient and control groups ($P > 0.05$).

In AS patients, occiput-to-wall distance, chest expansion, finger-floor distance, and modified Schober test are shown in Table 1. No correlation was found between these parameters of the disease and DPOAE findings. Of 28 AS patients, 27 were treated either with Sulphasalazine or methotrexate, or with a combination of Sulphasalazine and methotrexate. One patient was treated with non-steroidal anti-inflammatory drugs (NSAID) other than salicylates.

Table 1 Clinical features of the patients with ankylosing spondilitis

Parameters	Minimum	Maximum	Mean
ESR	3.00	75.00	30.42
CRP	2.00	102.00	28.78
Duration of disease (years)	2.00	40.00	11.64
Chest expansion	1.00	8.00	3.67
Occiput-wall	0.00	30.00	7.46
Finger-floor distance	0.00	65.00	24.50

Normal peak compliance, peak pressure, gradient, ear canal volume and acoustic reflexes obtained by immitance measures in the patients and controls. The pure-tone audiometry findings of the patient and controls are shown in Table 2. Because there was no air-bone gap in the participant, only bone conduction thresholds were taken into consideration. Pure tone thresholds of the patient and controls were significantly different in all frequencies (Fig. 1, $P < 0.05$). Sensorineural hearing loss was found in 10 patients (35%) as it was bilateral in seven and unilateral in three patients.

The DPOAE findings of the patient and controls are shown in Tables 3 and 4. There was no statistically significant difference between the levels of noise floor of the patients and controls ($P > 0.05$). The DPOAE responses of the patients and controls were significantly different in 3,000, 4,000, 5,000 and 6,000 Hz frequencies ($P < 0.05$).

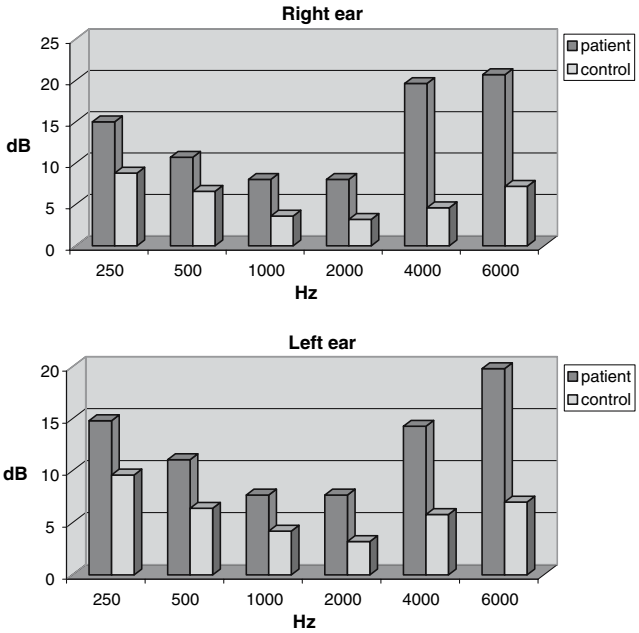

Fig. 1 Pure tone thresholds of the patient and controls were significantly different in all frequencies ($P < 0.05$)

Discussion

Although the etiopathogenesis remains obscure, AS is recognized as a chronic inflammatory disorder, which is strongly associated with human leukocyte antigen (HLA) B27 [1]. Autoimmune diseases are the result of an interaction between predisposing genes and triggering environmental factors, leading to loss of self-tolerance and an immune-mediated destruction of autologous cells and tissues. Genes in the HLA complex are among the strongest predisposing genetic factors. The HLA complex genes primarily involved are most often those encoding the peptide-presenting HLA class I or II molecules. A probable mechanism is preferential presentation by the disease-associated HLA molecules of peptides from autoantigens to T cells [10]. Immune mediated mechanisms are suggested by inflammatory histology, raised serum levels Ig A and acute phase reactants in AS. There is definitely a role for T cells in AS. In an immunohistologic study with obtained by sacroiliac biopsies, CD4+, CD8+ T cells and macrophages are present in inflamed sacroiliac joint [1].

Table 2 Pure tone audiometry findings of patient and control group

Frequency (Hz)	Patient group (right ear)			Patient group (left ear)		
	Range (dB)	Mean (dB)	SD	Range (dB)	Mean (dB)	SD
250	0–35	15	7.81	0–40	14.8	9.07
500	0–25	10.7	7.16	0–30	11	7.97
1,000	0–15	8	4.97	0–20	7.6	4.99
2,000	−5–35	8	8.85	−5–15	7.6	6.00
4,000	0–90	19.6	20.13	0–45	14.2	11.36
6,000	0–85	20.7	18.34	0–50	19.8	12.87
Frequency (Hz)	Control group (right ear)			Control group (left ear)		
	Range (dB)	Mean (dB)	SD	Range (dB)	Mean (dB)	SD
250	0–25	8.8	6.50	0–20	9.6	6.11
500	0–20	6.6	4.94	0–10	6.4	3.06
1,000	−5–10	3.6	3.68	0–10	4.2	3.12
2,000	−5–15	3.2	4.30	−5–10	3.2	3.78
4,000	−5–10	4.6	4.06	0–20	5.8	5.89
6,000	−5–20	7.2	5.78	−5–20	7	5.59

Extra-articular manifestations of AS can involve almost any organ or system. Anterior uveitis is the most frequent extra-articular manifestation, occurring in 25–30% of AS patients [11]. Other extra-articular manifestations are cardiac [12] and neurological involvement [13]. As the underlying pathology in AS is a chronic, inflammatory and immunologic basis, it can affect a variety of organs and tissues. This extra-articular manifestations support this idea. In this study, we demonstrated that inner ear or cochlea could be affected in AS.

Immunologic disturbances have been recognized to have a relation to many causes of auditory dysfunction [14]. Some autoimmune diseases such as systemic lupus erythematosus, ulcerative colitis, rheumatoid arthritis, autoimmune sensorineural hearing loss, relapsing polychondritis, disseminated vasculitis, polimyalgia

Table 3 DPOAE and noise floor findings of patient group

Frequency	*N*	Minimum	Maximum	Mean ± SD
1,000 Hz DPOAEs (dB SPL)	49	−7	24	7.44 ± 6.70
1,000 Hz Noise Floor (dB SPL)	49	−10	5	−4.67 ± 3.77
2,000 Hz DPOAEs (dB SPL)	51	−7	18	7.68 ± 6.94
2,000 Hz Noise Floor (dB SPL)	51	−10	4	−7.45 ± 2.86
3,000 Hz DPOAEs (dB SPL)	50	−9	17	2.32 ± 7.60
3,000 Hz Noise Floor (dB SPL)	50	−10	−2	−8.26 ± 1.80
4,000 Hz DPOAEs (dB SPL)	48	−9	17	2.14 ± 8.52
4,000 Hz Noise Floor (dB SPL)	48	−10	−4	−9.02 ± 1.57
5,000 Hz DPOAEs (dB SPL)	49	−9	18	1.77 ± 8.55
5,000 Hz Noise Floor (dB SPL)	49	−10	−5	−9.02 ± 1.42
6,000 Hz DPOAEs (dB SPL)	45	−9	10	−4.44 ± 5.17
6,000 Hz Noise Floor (dB SPL)	45	−10	−7	−9.42 ± 0.91

N Number of examined patients ear

Table 4 DPOAE and noise floor findings of control group

Frequency	*N*	Minimum	Maximum	Mean ± SD
1,000 Hz DPOAEs (dB SPL)	49	−10	23	8.53 ± 7.11
1,000 Hz Noise Floor (dB SPL)	49	−10	4	−4.02 ± 3.36
2,000 Hz DPOAEs (dB SPL)	50	−10	23	10.04 ± 6.65
2,000 Hz Noise Floor (dB SPL)	50	−10	0	−7.02 ± 2.76
3,000 Hz DPOAEs (dB SPL)	50	−4	21	9.68 ± 5.40
3,000 Hz Noise Floor (dB SPL)	50	−10	1	−7.62 ± 2.71
4,000 Hz DPOAEs (dB SPL)	50	−10	20	9.08 ± 6.73
4,000 Hz Noise Floor (dB SPL)	50	−10	−1	−8.36 ± 2.12
5,000 Hz DPOAEs (dB SPL)	50	−3	28	14.12 ± 7.33
5,000 Hz Noise Floor (dB SPL)	50	−10	−5	−9.16 ± 1.37
6,000 Hz DPOAEs (dB SPL)	49	−9	23	7.67 ± 7.42
6,000 Hz Noise Floor (dB SPL)	49	−10	−7	−9.42 ± 0.88

N Number of examined controls ear

rheumatica, and Hashimato's thyroiditis can cause sensorineural hearing loss [15]. Some mechanisms of auditory dysfunction are proven and some of them are postulated.

Many of the autoimmune diseases can cause vasculitis, resulting in a variety of secondary degenerative changes. Other possible mechanisms that may be related to the hearing loss include the development of hypertension with its simultaneous effects following renal involvement by the systemic condition and hyperviscosity problems arising either directly or indirectly from the condition. The most widely documented effects of autoimmune diseases resulting in sensorineural hearing loss are mediated by a vascular mechanisms [15]. Therefore, the cochlear hearing loss may result from vasculitis of the labyrinthine artery or its cochlear branch.

The stria vascularis is highly vascularized epithelial tissue, located on the lateral wall of the cochlea and playing a critical role in maintenance of the endocochlear (endolymph) electrical potentials (via potassium secretion) that power the cochlea in general, and outer hair cell activity in particular [16]. Underlying pathology in AS might have affected stria vascularis of the cochlea of patients with AS.

In a study, IgG antibodies against mesenchymal structures of the inner ear, the basement membrane of strial capillaries, the dark cell area, the spiral ligament and spiral lamina could be demonstrated [17]. Gussen described the temporal bone of a patient with polyarteritis nodosa that had perivascular infiltration of the labyrinthine artery, and fibrosis, bone formation and hydropic changes in the cochlea [18].

Some animal experiments have documented the existence of immunophatologic changes in the inner ear [19–21] the investigators showed an antigenic similarity between the cochlea and the kidney. The rat cochlea injected with antiglomerular basement membrane antibody was found to have a membrane-like exudates in the perilymphatic compartment of the cochlea. These studies suggested an immunologic cause of hearing loss in patients with kidney transplants.

Several studies demonstrated that the inner ear was the source of the antibody [22–24]. According to these studies the inner ear is capable of responding to antigen challenge. Harris and co-workers have shown a parallel rise of antibody titers over a 3-week period in guinea pigs immunized by either inner ear or peritoneal routes of antigen presentation [25]. These studies

indicate that the inner ear is an effective route of antigen processing that result in the acquisition of systemic humoral immunity as well as cellular immunity.

In an animal experimental study, Lewis and Wistar rats have been shown to develop sensorineural hearing loss with atrophy of the organ of Corti, spiral ganglion and vestibular degeneration, otospongiosis-like lesions in the tympanic annulus, and cochlear vasculitis. Both cellular and humoral responses to type II collagen were identified [26].

As a conclusion all of these studies, there seems to exist some relationship between biochemical, physiologic, and morphologic changes in the labyrinth in various immunologic and pathologic conditions. In our opinion, the range of variety of immunologic diseases is so wide, that the mechanisms of hearing loss are various.

Otoacoustic emissions are sounds found in the external auditory canal that originate from mechanical activity in the cochlea transmitted in a reversed direction through the middle ear and the tympanic membrane. These emissions arise from the vibratory motion of the outer hair cells. Attachment of the outer hair cells to the basilar membrane allows for a wave to be transmitted toward the stapedial footplate and ultimately into the external auditory canal. [27]

After the initial discovery of otoacoustic emissions by Kemp in 1978 [28] their clinical applications became wide-spread. At present, otoacoustic emissions are in wide-spread clinical practice, because this simple, cost-effective, noninvasive measure allows the clinician to probe the most sensitive workings of the inner ear in a frequency-specific manner.

Specifically, measurements of DPOAEs correspond closely to the physiological state of outer hair cells of the cochlea. Their main applications are the assessment of cochlear function to determine the site of pathological conditions associated with sensorineural hearing loss. DPOAEs, if normal, provide extremely strong evidence of normal cochlear function, regardless of audiometric data. The function of outer hair cells is integral to the overall sensitivity and frequency-selectivity of the auditory system. The auditory system can function without outer hair cells, but thresholds raise roughly 50 dB and frequency-selectivity decreases dramatically when the cochlea contains only inner hair cells [29].

In the review of the literature, we found only one clinical study related to hearing loss in patients with AS. In this study, audiometric examination and ABR was used for hearing assessment. As a conclusion of this study, the investigators found sensorineural hearing loss in 28.6% of the AS patients, and ABR findings were within normal limits. However there was little explanation about cause and possible mechanisms of hearing loss in patients with AS.

In conclusion, the cochlea is organized tonotopically. This means that the base end of the cochlea responds to high frequency sounds while the apical aspect responds to the low frequency sounds. In our study, based on the patients DPOAE findings, we found a damage of outer hair cells in patients with AS, and damaged outer hair cell regions was base and mid-portion of the cochlea.

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