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ORIGINAL ARTICLE

Involvement of Ear in Rheumatoid Arthritis. Prospective Clinical Study

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Objective: To investigate the relationship of the degree of hearing loss seen in rheumatoid arthritis (RA) and biochemical findings of the disease.

Materials and methods: This study was carried out with 44 RA patients and 44 voluntary healthy controls between November 2006 and June 2007. All members underwent audiometry and impedance audiometry. The duration of the disease, the drugs used for the disease and the biochemical findings of the patients were noted.

Results: Presbyacusis type sensorial hearing loss was detected in 27.3% of the patients and 15.9% in controls. Subclinic conductive hearing loss was seen in 56.8% of the patients and 25% of controls ($p<0.01$) and much more at frequencies of 500 Hz and 1000 Hz. The reason of this was seemed as the stiffness of the ossicular chain in patients.

Conclusion: Sensorineural hearing loss in RA is like presbyacusis and not statistically significant. However especially subclinic conductive pattern of hearing loss at low frequencies may be an indicator to predict the ossicular joint involvement in RA patients.

Key words: Rheumatoid arthritis, sensorineural hearing loss, conductive hearing loss, tympano-ossicular stiffness

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Introduction

The prevalence of autoimmune diseases is increasing recently. Rheumatoid arthritis (RA) has an important place in this wide spectrum of diseases. The hearing losses, that occur frequently in RA patients, are thought to be related to both the disease itself and the drugs employed [1].

RA is a multisystemic disease with a prevalence of 1% and characterised by destruction of cartilage, bone erosion and weakening, inflammation of diarthrodial joint synovial membranes leading to destruction in joint capsules, tendon and ligaments. Course of RA is a chronic, progressive, symmetric arthritis. The perivascular and synovial area infiltration by increasing of mononuclear and other cells leading to vasculitis which is the actual cause of synovitis [2]. Temporomandibular joint, larynx, cervical column and audiovestibular system are the areas involved in head neck region [3]. Incudomalleolar and incudostapedial joints are diarthrose joints, while the joint between the head of malleus and incus is saddle type, and the joint between the long process of incus and head of stapes is enarthrose type [4].

In many studies, patients with RA were compared with those without RA and sensorineural hearing loss (SNHL) up to 60% and lower rates of conductive hearing loss (CHL) and mixed type of hearing loss (MTHL) have been reported [2,5,6,7,10,11]. In addition, there are reports demonstrating that SNHL may develop by irreversible ototoxic effect of antirheumatismal drugs [1,8]. It has been thought that CHL occurs due to discontinuity in middle ear ossicles [1,9]. However, some authors have suggested that increase in the stiffness of ossicular system may give rise to CHL in RA [2,5].

In the present study, hearing functions and middle ear mechanics of patients with RA were examined and the relation between hearing functions and the characteristics of disease (duration and stage of disease, rheumatoid factor (RF) and anti-cyclic citrulline peptid (Anti-CCP) positivity, antirheumatoid

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treatment) were investigated and the results were compared with those in the literature.

Materials and Methods

This study was carried out with 44 RA patients (study group), which were diagnosed according to the criteria of American Rheumatology Association (1987), who referred to rheumatology clinic of Ministry of Health Ankara Training and Research Hospital and 44 volunteer healthy individuals (control group) between November 2006- June 2007. The study was carried out in accordance with the principles of Helsinki Declaration. The study was conducted in comply with the approval of the institutional ethical board (1649/25.04.2007).

The patient (study) and control groups underwent complete head and neck investigation and otoscopic examination. Patients and the members of the control group had normal tympanic membrane. Subjects with acute or chronic middle ear effusion, otitis media, or sequelae of otitis media (perforation, hyalinisation, retraction of tympanic membrane), Meniere's disease, otosclerosis, noise exposure, neurological disease, congenital hearing loss or other congenital diseases, audiovestibular complaints due to head or acoustic trauma or barotrauma, those who use drugs with known ototoxic effects currently or within the last three weeks, and who have other autoimmune rheumatologic diseases were excluded from the study. The distribution of age and sex characteristics were similar between patients and control groups.

Audiologic tests: These tests were carried out in noise-proof cabins (Industrial Acoustics Company, Inc, USA San Diego, CA), with AC 40 model clinical audiometer (Interacoustics Co, Assens, Denmark) and TDH 39 Mx-41/AR standard earphones. All tests were performed by the same investigator. Routine pure tone and speech audiometry were performed in both groups. Air conduction (AC) hearing thresholds were measured at 250 to 6000 Hz frequencies, and bone conduction (BC) hearing thresholds at 500 to 4000 Hz frequencies. Air bone gap (ABG) values, which are the difference in thresholds of AC and BC thresholds at 500 to 4000 Hz frequencies, were obtained. Sensorineural hearing was accepted as abnormal if the hearing threshold was higher than 20 dB at more one frequency for the tested ear [4]. How the hearing functions were affected by the duration and stage of the disease (according to Steinbrocker functional index) was discussed.

Impedance audiometry was used in order to establish the conduction and mobilization characteristics of middle ear. Tympanograms obtained at 226 Hz frequency using Az-26 clinical impedance device, were classified according to Jerger's types (A, As, Ad, B, C) [6,7]. Middle ear pressure, static compliance and acoustic reflexes were evaluated. Ipsilateral and contralateral stapedial reflexes were tested at probe tones between 75-110 dB.

Laboratory tests: RF and anti-CCP parameters, used as a sign of erosive joint disease in the follow up of the disease and evaluation of its prognosis, influencing the hearing and middle ear functions was evaluated.

Ototoxicity Anti rheumatoid drugs used in treatment were determined and evaluated with respect to ototoxicity.

Statistical analysis: Demographic statistics and descriptive statistics of measurements have been given. Means and proportional values were compared with Student's T test. When hearing should be compared with other parameters, Pearson's chi-square test was used. ($p<0.05$ values were considered as statistically significant).

Results

RA group including 40 women (90.9%) and 4 men (9.1%) (mean age 47.2±11.2) was compared with control group including 38 women (86.4%) and 6 men (13.6%) (mean age 44.7±10.8). Groups were similar ($p>0.05$).

The patients with RA had a mean disease duration of 9.8 years. According to Steinbrocker functional index, majority of RA patients was in stage 2 and none was at stage 4. Patients included in the study have not used salicylates, gold or D-penicillamine. They were taking single or combined antirheumatoid medical treatment. The distribution of clinical and laboratory findings is given in Table 1. No relation was found between occurrence of SNHL and CHL and age, sex, duration of disease, its stage, medical treatment, RF and anti-CCP.

Table 1. The distribution of descriptive clinical and laboratory findings of RAG

		RAG (n=44)	%
STAGE	1	14	31.8
	2	24	54.5
	3	6	13.6
Disease duration	0-10 year	29	65.9
	11-20 year	11	25
	21-30 year	4	9.1
RF	Negative	19	43.2
	Positive	25	56.8
Anti-CCP	Negative	8	18.2
	Positive	36	81.8
Drug intake	NSAID	33	75.0
	Steroid	13	29.5
	Sulfasalasine	22	50
	Hydroxychloroquine	22	50
	Methotrexate	27	61.4

RAG; rheumatoid arthritis group

Audiologic tests: Mean AC threshold, BC threshold and ABG values were determined for right and left ears in patient and control groups (Table 2). All threshold means were higher in study group than control group (except for left ABG at 2000 Hz,). However in the AC of patients with RA had marked hearing loss, for right ear at 500 Hz and 1000 Hz ($p<0.05$), and for left ear at 250 Hz ($p<0.05$), 500 Hz and 1000 Hz ($p<0.01$). Significant difference was found only in left ear at 500 Hz ($p<0.05$) in mean BC threshold. Significant difference was found in ABGs on right ear at 500 Hz ($p<0.01$) and 1000 Hz ($p<0.001$), and on left ear at 500 Hz and 1000 Hz ($p<0.001$). The mean pure tone AC threshold for 4 frequencies at the left ear is higher in patients than control group ($p<0.05$). There was no difference between speech discrimination scores between groups.

Table 2. Mean values and standard errors of AC, BC and ABG for each frequencies and compliance values in RAG and CG

	Right Ear (mean ± SEM)		Left Ear (mean ± SEM)				
	Frequency (Hz)	**CG (n=44)**	**RAG (n=44)**	**p value**	**CG (n=44)**	**RAG (n=44)**	**p value**
AC	250	12.5±1.2	14.0±1.4	NS	12.4±1.0	15.3±1.4	0.03
	500	10.3±1.0	13.9±1.5	0.025	9.6±0.8	14.9±1.4	0.002
	1000	9.0±0.9	12.7±1.4	0.032	8.3±0.8	12.8±1.4	0.007
	2000	11.4±1.0	14.3±1.7	NS	11.0±1.0	13.3±1.8	NS
	4000	15.3±1.8	15.6±2.3	NS	14.4±2.0	18.1±2.4	NS
	6000	23.1±2.3	24.1±2.7	NS	22.6±2.5	24.6±2.5	NS
BC	500	9.8± 1.0	11.6±1.5	NS	9.2±0.9	12.5±1.4	0.028
	1000	8.5± 0.8	10.0±1.5	NS	7.7±0.8	9.6±1.5	NS
	2000	10.4±1.0	13.4±1.6	NS	10.2±0.9	12.9±1.7	NS
	4000	15.0±1.7	16.1±2.2	NS	14.0±1.9	17.3±2.4	NS
ABG	500	0.6 ±0.2	2.3±0.5	0.006	0.4±0.2	2.4±0.4	0.001
	1000	0.7 ±0.3	2.7±0.4	0.001	0.6±0.2	3.2±0.6	0.001
	2000	0.9±0.3	0.9±0.3	NS	0.8±0.3	0.3±0.2	NS
	4000	0.3±0.2	0.5±0.2	NS	0.5±0.3	0.8±0.3	NS
PTA	(0,5-4 kHz)	11.5±1.0	14.4±1.6	NS	10.8±0.9	14.8±1.6	0.036
SDS %		96.5±0.4	93.2±0.8	NS	97.1±0.5	93.4±0.9	NS
Compliance (ml)		0.69±0.2	0.57±0.4	<0.05	0.69±0.3	0.55±0.3	<0.05

***AC,** air conduction; **BC,** bone conduction; **ABG,** air-bone gap; **RAG,** rheumatoid arthritis group; **CG,** control group; **NS,** not significant; **PTA,** pure tone average; **SDS,** speech discrimination score.*

SNHL was present in 12 of 44 patients (27.3%); 8 bilateral (18.2%) and 4 unilateral, so in 20 of overall 88 ears (22.7%). SNHL was present in 7 of 44 controls (15.9%); 3 bilateral (6.8%) and 4 unilateral, so in 10 of 88 normal ears (11.4%). The difference was not statistically significant (p>0.05).

In the present study, conductive hearing loss [4] defined as air-bone gap over 20dB in at least two frequencies was found neither in patient group nor in control group. Only in two patients, gap over 20dB was observed at one frequency. However, ABG over 5dB at two or more frequencies was present in 25 of 44 patients (56.8%); 13 bilateral (29.5%), 12 unilateral, so in 38 of 88 ears (43.2%). In the control group, CHL was demonstrated in 11 subjects (25%); 4 bilateral (9.1%) and 7 unilateral, so in 15 of 88 control ears (17%). The difference in CHL between controls and the patients was statistically significant (p<0.01).

MTHL was established in unilateral ear of 2 patients (4.5%) and 2 controls.

Results of SNHL and CHL distribution of control and patient groups is given in Table 3. SNHL was observed at high rates for 2000 Hz and 4000 Hz both in control group (33.3% and 37%) and patient groups (28.3% and 31.7%). The distribution was similar in both groups so insignificant (p1 and p2 >0.05). ABG rates for each frequencies were distributed equally in control group (p3>0.05). In patient group, ABG rates were as follows; 39% at 500 Hz, 43.1% at 1000 Hz, 8.5% at each 2000 Hz and 4000 Hz with marked predominance at 500 Hz and 1000 Hz (p3<0.001). CHL rate at 500 Hz was significantly higher in RA group than control group (p1<0.05).

Table 3. The distribution of SNHLs and CHLs in RAG and CG

		(SNHL)				(CHL)		
Frq	**CG (R+L) (ears=27)**	**RAG (R+L) (ears=60)**	**p1 value**	**p2 value**	**CG (R+L) (ears=34)**	**RAG (R+L) (ears=82)**	**p1 value**	**p2 value**
500	4+2=%22.2	6+6=%20	NS	NS	4+2=%17.6	16+16=%39	<0.05	<0.001
1000	1+1=% 7.4	6+6=%20	<0.05		5+5=%28.6	18+18=%43.1	NS	
2000	5+4=%33.3	10+7=%28.3	NS	NS	6+5=%32.4	5+2 =% 8.5	<0.01	<0.001
4000	5+5=%37	11+8=%31.7	NS		3+4=%20.6	2+5 =% 8.5	NS	
p3 value	<0.001	<0.01			NS	<0.001		

SNHL: *sensorineural hearing loss,* ***CHL:*** *conductive hearing loss,* ***RAG:*** *rheumatoid arthritis group,* ***CG:*** *control group,* ***Frg:*** *frequency,* ***NS:*** *not significant*

p1: *Statistics of t he RAG versus CG for each frequencies*

p2: *Statistics of the RAG versus CG in each coupled frequencies as (500Hz+1000Hz) and (2000Hz+4000Hz)*

p3: *Statistics of coupled frequencies as (500Hz+1000Hz) versus (2000Hz+4000Hz) for both RAG and CG*

Tympanometric compliance mean values were found as 0,57±0,36 and 0,55±0.28 ml at right and left ears in the patients, while the corresponding values were 0.69±0.11 and 0.69±0.27 ml in the control group with a statistically significant difference (p<0.05). There was no correlation between the duration and stage of disease, RF and anti-CCP positivity and mean tympanometric compliance values.

The distribution of abnormal tympanograms in patients and control group is demonstrated in Table 4.

Type As tympanogram (value of static compliance ≤0.3ml) was observed in 13 ears (14.7%) of 10 patients (22.7%), 4 bilateral while in control group, it was unilateral in 2 (4.5%) subjects, and the difference was significant (p<0.05). Type Ad tympanogram was found unilaterally in 2 patients and 1 control (p>0.05). All of the remaining ears had type A tympanogram. No statistically significant relation was found between Type As tympanogram and the duration and stage of RA, drugs used, RF and anti-CCP positivity, and hearing loss (p>0.05).

Table 4. Abnormal type of tympanograms in RAG and CG (number of ears)

	Tympanogram	Normal Hearing	SNHL	CHL	Mixed HL	Total
RAG	A_s	4	2	6	1	13*
	A_d	1	-	1	-	2
CG	A_s	1	-	1	-	2*
	A_d	-	-	1	-	1

RAG; *rheumatoid arthritis group,* ***CG;*** *control group,* ****;*** *p<0.05*

SNHL; *sensorineural hearing loss,* ***CHL;*** *conductive hearing loss*

Stapedial reflex could not be elicited in 5 patients and 4 control ears (p>0.05).

Discussion

Although SNHL is frequently emphasized in these patients with RA, both SNHL and less commonly CHL and MTHL have been reported [1,5,6,7,10]. SNHL has been reported in the literature at rates up to 60% [5,6,8,11]. In the present study, SNHL was established at the rate of 27.3% in RA patients (in 12 of 44 patients, 8 bilateral) and 15.9% in control group. Hearing loss was bilateral in 2/3 of our patient group. For all measured frequencies, although mean AC and BC thresholds were higher in patients than in controls, the only significant difference was on BC at 500 Hz in left ear (table 2).

The pathophysiology of hearing loss in patients with RA is not completely known. Although retrocochlear involvement has been reported by Magaro et al. [12], it is reported to be of cochlear origin in the majority of the literature, and inner ear structures are influenced due to vasculitis, neuritis and ototoxic medication employed in RA treatment [1,8]. Based upon the idea that immune complex-mediated vasculitis of the inner ear or auto antibodies against inner ear antigenic epitopes may lead to SNHL, Takatsu et al. [7] could not demonstrate humoral and cellular hyperactivity against autoimmunity to type II collagen and inner ear antigens in otosclerosis and Meniere's disease. However, they reported that SNHL in their cases, was associated with high ESR (pointing out chronic inflammation and tissue injury), plasma interleukin-6 and plasma matrix metalloproteinase-3 among proinflammatory cytokines. Ferrara et al. [4] and Magaro et al. [12] stated that SNHL may develop in the progressing stages of the disease through anomalous compressive effect on the labyrinth with the stiffness in ossicular chain and with chemical injury in inner ear caused by inflammatory mediators of inflamed stapedo-ovalar joint. Many investigators have suggested that SNHL was related to rheumatoid nodules, active disease, stage of the disease, rheumatoid factor (RF), anti-CCP, and age [7,8,10,13]. Potential ototoxic effects of immunosuppressive and anti inflammatory drugs used in RA treatment are not frequent. Sporadic cases have been published due to side effect of regular salicylates, hydroxychloroquine, and methotrexate usage [1,2,10,13,14]. In the large prospective study by Kastanioudakis et al. [8] no correlation was found between drug intake and SNHL (NSAIDs except salicylates, hydroxychloroquine-plaquenil, D-penicillamine, methotrexate). In our patient group, none of the cases has been at stage 4 was present and none of them received salicylate treatment. No significant relation could be found between SNHL, and age and sex of our patients, duration and stage of disease, SDS, acoustic reflexes, RF, anti-CCP and the antirheumatismal drugs they use (NSAID, steroid, sulfasalazin, hydroxychloroquin, methotrexate).

There are studies reporting that SNHL developing in RA is more severe in low frequencies [5] while there are also autors reporting that it is observed at high frequencies [1,11], and even that it correlates with age and it can be ascribed to presbyacusis rather than RA and drug intoxication [7,8]. On this controversial issue, Colletti et al [2] suggested that when rheumatoid ossicular joint fixation occurs, inner ear protective mechanism is impaired and in the long term hairy cells of inner ear may be injured by being exposed to intrinsic and extrinsic traumas. In response to this, Raut et al [5] suggested that this theory proposes that SNHL will occur in higher frequencies, which is contrary to their findings. The distribution of SNHL in patients and controls (Table 3) was similar except for

1000 Hz. In both groups, SNHL displayed a significant dominance in 2000 Hz and 4000 Hz, which are high frequencies. Although mean age of patients and controls with SNHL was higher than that of those without SNHL, the difference was not significant ($p>0.05$). The similarity of distribution of patient and control groups, bilateral SNHL at high frequencies and the higher rate of SNHL in patient group, although the difference is not significant, (27.3% vs. 15.9%) may be interpreted in favour of presbyacusis or as the acceleration of this process by RA.

In controlled studies, conductive hearing loss prevalence has been reported to be lower than SNHL between 0-24.3% in RA patients [2,10,15,16]. In a study, 5 dB air bone gaps were accepted as CHL [14]. In another report, gap values over 5dB have been investigated and increased mixed type hearing loss and "a multifocal involvement of the auditory system in patients with RA" have been attracted attention (10). In the present study, in 25 patients with CHL over 5 dB it was established at the rate of 56.8% with 13 bilateral (29.5%) in 38 of 88 ears (43.2%). In the control group, the corresponding rates were respectively 25%, 9.1%, 17% with a statistically significant difference ($p<0.01$). In addition, AC and ABG mean values were statistically higher at 500 and 1000 Hz, as low frequencies. There was not a significant difference between MTHL values in 2 patients (4.5%) and 2 controls (4.5%).

Tympanometric investigations have been made in order to explain CHL in the literature. When conduction component is not obtained at necessary audiometric size, increased stiffness [1,2,6,10,17] or discontinuity of ossicular chain [5,9,10] were implicated in order to reveal subclinical involvement. The involvement of incudomallear and incudostapedial joints, which are real diarthrosis type, may lead to CHL, in the process of RA. Vasculitis, which is another characteristics of disease, may lead to inadequate perfusion in the long process of incus and necrosis and then ossicular discontinuity [1,2]. Colletti et al. [2] could not demonstrated CHL, although showed 6.6% decreased and 18.3% increased stiffness in their cases. They explained this phenomenon as follows; in RA increased stiffness in joints does not influence sound conduction to cochlea and ossicles are already fixed during sound transmission, hence normal hearing is possible in spite of increased stiffness.

In the present study, in the tympanometric examination made in order to evaluate high sublinical CHL rates; and mean tympanometric compliance values were found to be significantly lower in both ears of the patients than those of the controls ($p<0.05$). Abnormal tympanogram was found in 15 ears of 12 patients (17%) and 3 ears of 3 controls (3.4%) ($p<0.01$). Increased (22.7%) and decreased stiffness (4.5%) was established in our cases. ($p<0.05$). Although there was increased stiffness in RA patients with hearing loss, no significant difference was found in the distribution of patients with abnormal tympanogram (Table 4).

In comparison of ABG between patient and control groups, it was established that although the distribution between frequencies was equal in control group ($p>0.05$), there was a predominance at 500 Hz and 1000 Hz in both ears of RA patients (Table 3). ABG found in low speech frequencies was more preponderant than the other frequencies in patient group itself and controls ($p<0.001$).

The fact that mean duration of disease was 9.8 years in our patients and their being mostly at early stages (86.3%, stage1-2), and the appearance of significant decrease in compliance and occurrence of Type As tympanograms can be interpreted, as Colletti suggested, as follows; RA even in its early stages when distinct hearing loss is not present yet, may influence middle ear mechanics at low frequencies by increase in stiffness rather than discontinuity.

However, in recent studies; it was concluded that in RA patients with demonstrated transient evoked otoacoustic emissions (TEOAEs) decrease or absent, may be represent an early stage of hearing loss, vasodilator treatment and antioxidant drugs may be useful for protection of the inner ear [18,19]. In contrast to this, in another study; there was no difference found in objective audiometric measurements in patients with RA compared with non-RA control subjects [20].

Conclusion

As evaluated through this study, hearing loss is a common complaint in patients with RA, and it should be followed by history, routine audiometry and impedancemetry during the course of the disease. SNHL at high frequencies is similar to presbyacusis and usually occurs bilaterally. Before the appearance of distinct hearing loss, low frequency subclinical CHL may occur in association with the involvement of

ossicular joints and ossicles. For the determination of this condition, low compliance values and monitorization of tympano-ossicular stiffness may be helpful. It is possible to increase the quality of life by early detection of otologic effects of the disease and planning of rehabilitation with progressing disease. RF and anti-CCP positivity, duration of the disease, stage of the disease, and antirheumatismal medical treatment are not seemed effective on hearing loss and middle ear functions: However this conditions should be evaluated in larger studies.

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