



The Effect of Rheumatoid Arthritis on Middle and Inner Ear Functions

Original Investigation

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Abstract

Objective: To investigate the middle and inner ear functions, and efferent auditory systems in patients with rheumatoid arthritis (RA).

Methods: Thirty-five RA patients and 40 control subjects participated in the study. Pure-tone audiometry, high-frequency audiometry, multifrequency tympanometry, transient evoked otoacoustic emissions, and contralateral suppression tests were administered to all participants.

Results: Pure-tone hearing thresholds of RA patients were significantly higher at all frequencies except for 2000 Hz, 14,000 Hz, and 16,000 Hz in the right ear and 16,000 Hz in the left ear ($p < 0.05$). Resonance frequency values of RA patients were statistically significantly lower than those of the control group ($p < 0.001$). Emission amplitudes obtained with contralateral acoustic stimulation were significantly lower at 1400 Hz frequency in both groups than without contralateral acoustic stimulation ($p < 0.05$). While contralateral suppression was observed at all frequencies in the control group, no suppression occurred at 2800 Hz and 4000 Hz in RA patients.

Conclusion: The results obtained in this study demonstrated the presence of hearing dysfunction in patients with RA. When a patient is diagnosed with RA, an audiological evaluation should be made, and the patient should be informed about the possibility of audiological involvement.

Keywords: Rheumatoid arthritis, hearing loss, inner ear, middle ear, audiology

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Cite this article as: Demir S, Pamukcu M, Erbek SS. The Effect of Rheumatoid Arthritis on Middle and Inner Ear Functions. Turk Arch Otorhinolaryngol. 2024; 62(1): 14-20

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Received Date: 07.02.2024

Accepted Date: 30.04.2024

DOI: 10.4274/tao.2024.2024-2-2

Introduction

Rheumatoid arthritis (RA) is a long-lasting inflammatory autoimmune disease that affects multiple synovial joints. CD4(+) T-cells and monocytes pass from vessels into inflamed synovial tissue and fluid, characterizing the disease. The etiology and pathogenesis, however, remain unknown (1). It is known that diarthrodial synovial joints are more affected by RA. The ossicles malleus, stapes, and incus, which grow together sequentially in the

middle ear, are diarthrodial joints and therefore may be affected by RA (2, 3).

Ear disorders are described in up to 85.71% of patients with RA with a higher prevalence of sensorineural hearing loss (SNHL) than conductive hearing loss (CHL) and/or mixed hearing loss (MHL) (4-6). The prevalence of CHL in patients with RA has been reported to range from 0% to 25% (1, 4). It has also been reported that sudden SNHL could occur in RA patients (7-9). Some studies suggest that



there is no association between hearing loss (HL) and RA (10-14).

Auditory efferent function is assessed using contralateral suppression of cochlear responses, and otoacoustic emissions (OAE) (15). Transient evoked otoacoustic emission (TEOAE) can be used to study the function of the medial efferent system by analyzing the levels of responses obtained in the presence of noise and without noise (16). TEOAE suppression is considered an important, rapid, and non-invasive clinical procedure for evaluating cochlear function and the functioning of the efferent medial olivocochlear system (MOC) (17).

Although studies in the literature have shown an association between RA and hearing disorders, there is insufficient data on the location of the pathology causing HL. Studies evaluating middle ear and inner ear functions together are very limited. There is no study examining the olivocochlear efferent neural pathway in patients with RA. In this study, we investigated whether RA affected middle and inner ear functions.

Our study aimed to comprehensively evaluate the middle and inner ear functions and efferent auditory system of RA patients with pure-tone audiometry, high-frequency audiometry, impedancemetry, multifrequency tympanometry (MFT), TEOAEs, and contralateral suppression testing.

Methods

The study was approved by the Clinical Research Ethics Committee of the Medical Faculty of Başkent University (project no: KA15/538, date: 23.12.2015, decision no: 15/111) and all participants signed an informed consent form.

The sample size was calculated by power analysis by adopting a two-tailed type I error of 0.05 and a power of 0.80 as approximately 35 patients in each group. The study group included 35 patients (70 ears) in an age range of 20–60 years, and RA diagnoses were made according to 1987 ACR criteria (18). The control group included 40 healthy age- and sex-matched volunteers (80 ears).

Pure-tone audiometry, high-frequency audiometry (8000–16,000 Hz), immittancemetry, MFT, TEOAEs, and contralateral suppression tests were administered to all participants. Before the audiological examination, all cases underwent a complete ear, nose, and throat examination. Medications taken alone or in combination by the patients with RA consisted of non-steroidal anti-inflammatory drugs, sulfasalazine, methotrexate, and steroids. None of the subjects were undergoing treatment with salicylates, sedatives, tranquilizers, or vestibular suppressants, and none consumed alcohol.

The inclusion criteria for both groups were normal findings in the ear, nose, and throat clinic examination, type A tympanogram in the electroacoustic immittancemetry test, and obtaining ipsilateral and contralateral reflexes. The patients included were those with no history of systemic, chronic, or autoimmune disease other than RA.

The exclusion criteria for both groups were the presence of pathology in the outer ear canal, the tympanic membrane, and/or the middle ear; the use of ototoxic drugs; a history of acoustic and/or physical trauma; having an ear disease that could permanently affect hearing thresholds; or a history of ear surgery.

Audiological Evaluation

We conducted pure-tone audiograms in soundproof cabins using the Clinical Audiometer AC-40 (Interacoustics A/S, Assens, Denmark). Pure-tone absolute thresholds were obtained at pure-tone frequencies between 125 and 8000 Hz. High-frequency hearing thresholds were determined at frequencies between 9000 and 16,000 Hz. Bone conduction thresholds were obtained at 250, 500, 1000, 2000, and 4000 Hz. We calculated pure-tone averages (PTAs) for frequencies of 500, 1000, and 2000 Hz. Northern and Downs' (2002) classification was used to classify HL (19). A PTA of 15 dB or less was considered normal hearing.

Acoustic Impedancemetry

Subjects underwent immittance measurements with a GSI TympStar Version 2 (Grason 05 Stadler Inc., MN, USA) middle ear tympanometer. Ipsilateral and contralateral reflexes were tested at 500, 1000, 2000, and 4000 Hz.

Multifrequency Tympanometry

In this procedure, a probe was inserted into the ear canal and the pressure was maintained at a constant level. Tympanograms were recorded using probe frequencies from 250 Hz to 2000 Hz in 50 Hz intervals.

Measurement of TEOAE with MOC Reflex

TEOAE tests (Titan; Interacoustics A/S Assens, Denmark) were performed in a quiet room. During the measurements, the stimulus severity was 80 ± 3 dB SPL; reproducibility over 65%; frequency bands 1000, 1400, 2000, 2800, 4000 Hz and stimulus stability over 70% in the tested frequency. To investigate TEOAE suppression, a white noise was presented contralateral to the tested ear at 70 dB SPL. The test was applied in two steps. TEOAEs were recorded without and with contralateral noise. The results were recorded to be able to evaluate whether there was contralateral suppression.

Statistical Analysis

SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For continuous variables

with normal distribution, the Student's t-test was conducted, otherwise the Mann-Whitney U test was used. A paired t-test was used to compare TEOAE values before and after contralateral acoustic stimulation (CAS) in each group. Any p-value less than 0.05 was considered statistically significant.

Results

The mean age was calculated as 44.3±10.4 years in the RA patients and 41.4±12.5 years in the healthy control group (p<0.05).

Audiological Results

A total of 150 ears were evaluated, with 70 ears in the patient group and 80 ears in the control group. The hearing thresholds of the patient and control groups were separately compared at 125–16,000 Hz for both ears. The pure-tone hearing thresholds of the right and left ears of the patient and control groups were compared separately at 125–16,000 Hz. When the RA patient group's air and bone conduction hearing thresholds were examined, SNHL was determined at the rate of 15.7% in 11 ears of 7 patients as bilateral in 4 patients and unilateral in 3 patients according to PTAs.

The pure-tone hearing thresholds of the RA patients were significantly higher at all frequencies except for the frequencies of 2000 Hz, 14,000 Hz, and 16,000 Hz in the right ear and 16,000 Hz in the left ear (Figures 1, 2; p<0.05).

Multifrequency Tympanometry Results

Comparisons of the resonance frequency values for both ears in both groups are shown in Table 1. Resonance frequency values obtained in the RA patients were statistically significantly lower than those of the control group (p<0.05). The resonance frequency values of the patient and control groups were 748.8±188.0 Hz and 830.0±122.3 Hz for the right ear and 772.8±157.8 Hz and 847.5±140.9 Hz for

the left ear, and the difference was statistically significant (p<0.001).

OAE and MOC Results

In the comparison of the TEOAE results of the two groups, emission results of RA patients were found statistically significantly lower at 1000 Hz, 2000 Hz, 2800 Hz, and 4000 Hz compared to the control group (p<0.05) (Table 2).

To examine the effects of the disease on the MOC efferent system activity, comparisons of the results of the TEOAE measurement were made before and during CAS application (Table 3). In the measurements taken in the RA patient group while applying CAS, suppression occurred at 1000, 1400, and 2000 Hz but not at 2800 Hz and 4000 Hz, and

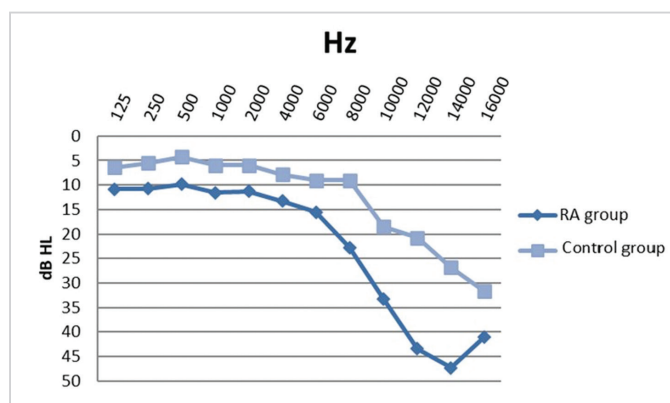


Figure 2. 125–16,000 Hz left ear pure sound hearing threshold averages of the groups

RA: Rheumatoid arthritis, Hz: Hertz, dB: Decibel

Table 1. Comparison of resonance frequency averages of the groups

	Right		Left	
	RA Mean (±SD)	Control Mean (±SD)	RA Mean (±SD)	Control Mean (±SD)
RF	748.8 (188.0)	830.0 (122.3)	772.8 (157.8)	847.5 (140.9)
p-value	<0.001**		0.001*	

RA: Rheumatoid arthritis, RF: Resonance frequency, SD: Standard deviation, *Student t-test, **Mann-Whitney U test were used

Table 2. Comparison of TEOAE results of the groups

Frequency (Hz)	RA Mean (±SD)	Control Mean (±SD)	p-value*
1000 Hz	18.1±6.3	20.8±5.4	0.005
1400 Hz	19.0±6.6	20.9±5.4	0.067
2000 Hz	15.1±4.9	16.7±4.2	0.031
2800 Hz	11.4±4.9	13.5±4.4	0.005
4000 Hz	11.6±4.2	13.4±4.9	0.018

TEOAE: Transient evoked otoacoustic emission, RA: Rheumatoid arthritis, SD: Standard deviation, Student t-test was used, *p<0.05

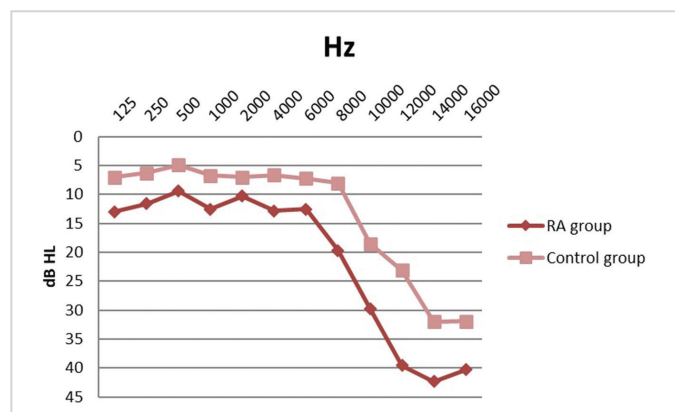


Figure 1. 125–16,000 Hz right ear pure sound hearing threshold averages of the groups

RA: Rheumatoid arthritis, Hz: Hertz, dB: Decibel

the difference was determined to be statistically significant ($p < 0.001$).

Suppression was obtained at all frequencies in the control group and the difference was statistically significant (Table 4, $p < 0.0001$).

Discussion

In the presented study, SNHL was found in 15.7% of the RA patients. The pure-tone hearing thresholds of RA patients were higher than those of the control group at all frequencies between 125 Hz and 16,000 Hz. The resonance frequency values of the RA patient group were statistically significantly lower than those of the control group. The TEOAE results of both groups were compared, and except for the 1400 Hz frequency, the amplitude values of the emission responses of the RA patients were statistically significantly lower than those of the control group. In the measurements during CAS application, suppression occurred at all frequencies in the control group, whereas in the patient group, suppression occurred only at the 2800 Hz and 4000 Hz frequencies.

RA may affect the temporomandibular joint, the larynx, the cervical spine, and the audiovestibular system in the head and neck region (2). RA can lead to CHL due to pannus formation in the incudostapedial joint and the incudomalleolar joint between the ossicles in the middle ear,

which leads to the accumulation of synovial elements on the disc and articular surface (20). Some studies have shown a higher prevalence of HL, especially of the sensorineural type, in RA patients (4-6, 21-29). The exact mechanism linking RA and SNHL is still controversial, but several possible mechanisms have been proposed. Damage to the cochlea is one of the most frequently mentioned mechanisms (3, 13, 23). Some authors have suggested that the involvement of extra-articular disease is caused by vasculitis, neuritis, as well as cochlear and cochlear nerve involvement (10, 21). While most studies have found no evidence of retro-cochlear effects of RA, Magaro et al. (21) reported such findings. Colletti et al. (3) stated that in rheumatic fixation of the ossicular joint, the protective mechanism of the inner ear is impaired, and the hair cells of the inner ear may be damaged because of long-term exposure to intrinsic and extrinsic trauma. A previous study reported that HL was sensorineural at 8000 Hz and the loss of acoustic reflex was associated with the effects on the middle ear (30). The destruction of cochlear cells or the accumulation of immune complex deposits in the inner ear can lead to HL by triggering the autoimmune process (21, 22). There are publications in the literature reporting that drugs used in the treatment of RA could affect the inner ear (10, 20). In another study, Kastanioudakis et al. (22) did not find a correlation between antirheumatic drugs and inner ear disorders. In our study, the time between the diagnosis of the disease and the time the tests were performed, the medications used, and their duration varied. Therefore, no definitive interpretation can be made as to whether the SNHL detected in our patients was due to the disease affecting the inner ear or to the medications they used. Additionally, none of our patients were being treated with salicylates, which can cause cochleovestibular dysfunction (20).

Several studies have reported varying rates of HL in patients with RA. García Callejo et al. (6) found that 42.7% of their participants experienced HL between 500 and 3000 Hz frequency range. The researchers compared patients with RA to healthy controls and found a significant difference. Furthermore, they discovered that 96% of HL cases were sensorineural, while the remaining 4% were conductive (6). A study found that 12.5% of RA patients without HL developed it within a year, with 90% being sensorineural and 10% conductive (26). Accordingly, 12.5% of the patients developed HL within one year, out of which 90% were sensorineural and the remaining 10% conductive. Lobo et al. (12) reported that 46.5% of RA patients and 30.4% of controls had HL. In 80% of the RA patients and 85.7% of the control subjects with HL, the HL can be described as sensorineural (12). Galarza-Delgado et al. (28) reported that SNHL occurred at 500–3000 Hz in 36.8% of the patients with RA, at 4000–8000 Hz in 68.4%, and at 10,000–16,000 Hz in 94.9%. Treviño-González et al. (31) reported that SNHL was observed in 43.5% of patients at a sensitivity to pure-tones of 125 to 8000 Hz, in 94.0% of patients at a tone

Table 3. TEOAE values before contralateral acoustic stimulation and during contralateral acoustic stimulation in RA patients

Frequency (Hz)	TEOAE before CAS Mean (\pm SD)	TEOAE during CAS Mean (\pm SD)	p-value*
1000 Hz	18.1 (6.3)	14.7 (6.4)	<0.001
1400 Hz	19.0 (6.6)	18.1 (5.9)	<0.001
2000 Hz	15.1 (4.9)	14.5 (5.3)	<0.001
2800 Hz	11.4 (4.9)	11.7 (5.0)	No suppression
4000 Hz	11.6 (4.2)	12.3 (4.4)	No suppression

CAS: Contralateral acoustic stimulation, TEOAE: Transient evoked otoacoustic emission, RA: Rheumatoid arthritis, SD: Standard deviation, Hz: Hertz, *Paired sample t-test was used

Table 4. For the control group, TEOAE values before contralateral acoustic stimulation and during contralateral acoustic stimulation

Frequency (Hz)	TEOAE before CAS Mean (\pm SD)	TEOAE during CAS Mean (\pm SD)	p-value*
1000 Hz	20.8 (5.4)	16.2 (5.3)	<0.001
1400 Hz	20.9 (5.4)	18.8 (5.3)	<0.001
2000 Hz	16.7 (4.2)	16.0 (4.5)	<0.001
2800 Hz	13.5 (4.4)	12.5 (4.5)	<0.001
4000 Hz	13.4 (4.9)	13.2 (4.0)	<0.001

CAS: Contralateral acoustic stimulation, TEOAE: Transient evoked otoacoustic emission; SD: Standard deviation, Hz: Hertz, *Paired sample t-test was used

threshold of 10,000 to 16,000 Hz in the right ear, and in 95.7% in the left ear. Another study found that 69.8% of 53 RA patients had SNHL at high frequencies (10,000–18,000 Hz), while only 43% reported SNHL on standard audiometry at 125–8000 Hz (27). There are also studies looking at MHL in RA patients. Kakani et al. (32) found MHL in 4% of their RA patients. Ozcan et al. (5) reported 35.1% SNHL, 24.3% CHL, and 10.8% MHL. Almasi et al. (29) reported that the frequency rates of CHL in the left and right ears were 2% and 5%, respectively, and the rates for SNHL were 55% and 61%, respectively. In addition, the percentage of HL in low-, mid-, and high-frequency ranges was 18%, 19%, and 57%, respectively. The presence of MHL suggests multifocal involvement of the auditory system in RA (5). Some studies suggest that there is no link between HL and RA disease (10-14). The most common HL reported in the literature is SNHL. Recent studies have reported that sudden SNHL could occur in RA patients (7-9). In addition, Wang et al. (7) reported that HL recovery was difficult in sudden SNHL patients with RA, and its prognosis could worsen as the course of RA lengthened. In our study, we observed SNHL in 15.7% of the RA patients, as consistent with the literature, and the pure-tone hearing thresholds of these patients were higher than those of the control group in the pure-tone and high-tone audiometry measurements at all frequencies between 125 Hz and 16,000 Hz. Except for the 2000 Hz, 14,000 Hz, and 16,000 Hz frequencies in the right ear and 16,000 Hz in the left ear, this difference was statistically significant at all frequencies. From these findings, it can be concluded that the cochlea is a target organ in RA.

In studies of RA patients, lower OAE responses were obtained compared to the control subjects, or in the majority of cases, not at all. Halligan et al. (14) found no differences in TEOAE, whereas Dikici et al. (10) and Salvinelli et al. (4) observed significantly lower TEOAE amplitudes in patients with RA compared with controls. Lobo et al. (12) found that RA patients had reduced response amplitudes to stimulation compared to controls at all frequencies tested, with statistical significance only at 2 kHz in both ears. Murdin et al. (33) found no TEOAE in a vast majority of their RA patients. It was hypothesized that this could be an indication of early symptomatology of HL. When the TEOAE results of both groups were compared in our study, the emission responses of the RA patients were significantly lower at the amplitude levels of 1 kHz, 2 kHz, 2.8 kHz, and 4 kHz compared to those of the control group. From these findings, it can be concluded that the outer hair cells could be affected by the disease process.

In studies using MFT in RA patients, abnormal resonant frequencies were found in RA patients compared to control groups. In a study by Colletti et al. (3) resonance frequency was examined with MFT in 30 RA patients and 48 control subjects. Abnormal resonance frequency values were

found in 12 RA patients (40%), while normal resonance frequencies in the range of 900–1250 Hz were found in the control group. Biasi et al. (34) studied 30 RA patients and 48 control subjects and found normal resonance frequencies between 800 and 1250 Hz in the control group and abnormal resonance values in 11 of the RA patients. In these studies, it was reported that the abnormal resonance frequency values in RA patients could be due to an impairment of ossicular mechanics related to the involvement of the incudomalleolar and incudostapedial joints. Pascual-Ramos et al. (26) reported a normal tympanogram in 93 patients (82%), although high-frequency tympanometry was abnormal in 80 patients (71.4%). In our study, the resonance frequency values of the patient group were statistically significantly lower compared with those of the control group. We think that the low-frequency values in the patient group were related to inflammation of the soft tissue and ligamentous structures. However, further studies are needed to investigate the physiology of low resonance frequency in RA patients.

Although there are several studies in the literature on the MOC reflex, there are no studies on RA patients in this regard. However, there are findings indicating that outer hair cell functions are impaired in RA patients. In our study, while contralateral suppression occurred at all frequencies in the control group, no suppression was observed at 2800 Hz and 4000 Hz in the patients with RA. According to these results, the contralateral suppression ability in RA patients associated with the efferent auditory system is impaired at 2800 Hz and 4000 Hz, so it can be said that RA disease has an impact on the function of the efferent auditory system. However, further studies are needed to show the sensitivity of the peripheral auditory system in RA patients.

RA activity and its effects on hearing is a controversial issue. Murdin et al. (33) found no relationship between hearing thresholds and markers of disease activity or other rheumatological parameters. Salvinelli et al. (4) found no differences in hearing thresholds between active and inactive RA patients and between RA patients and controls. Ozcan et al. (5) could not detect a relationship between hearing thresholds and disease activity and other rheumatological parameters. Yilmaz et al. (25) reported that while there was a slight increase in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor values of patients with suspected inner ear pathology, these differences were not found to be statistically significant. There are studies in the literature showing a relationship between disease activity and SNHL (1, 10, 21). Takatsu et al. (1) showed that the frequency of SNHL was associated with ESR and plasma concentrations of IL-6 and matrix metal loproteinase-3. Dikici et al. (10) concluded that higher ESR and CRP levels were associated with HL. The disease activity of the patients participating in the study, diagnosis/symptom duration, laboratory parameters, and the effects of

the treatments they received on hearing were not examined. A meta-analysis is needed to draw definitive conclusions in this area. Another limitation of our study is that we only measured HL at one point in time, without considering its progression over time. Therefore, we were unable to properly analyze the effects of treatment over time.

Conclusion

The presented study found that RA patients experienced deterioration in pure-tone hearing thresholds, a decrease in resonance frequency values, low amplitude values in emission responses, and high-frequency distortion. These findings demonstrate that middle and inner ear functions are impaired in RA patients. Therefore, patients diagnosed with RA should undergo audiological assessment and be informed of the possibility of otologic involvement.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of the Medical Faculty of Başkent University (project no: KA15/538, date: 23.12.2015, decision no: 15/111).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authorship Contributions

Surgical and Medical Practices: S.D., M.P., S.S.E., Concept: S.D., S.S.E., Design: S.D., S.S.E., Data Collection and/or Processing: S.D., M.P., Analysis and/or Interpretation: S.D., M.P., S.S.E., Literature Search: S.D., Writing: S.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- Although studies in the literature have shown the presence of a relationship between RA and impaired hearing, there is insufficient data about the location of the pathology that causes hearing loss.
- There are no studies evaluating the olivocochlear efferent neuronal pathway in patients with RA.
- The results of the presented study show that deteriorated middle and inner ear functions could be related to RA, and it is important to evaluate the effect of RA on middle and inner ear functions with a comprehensive test battery.

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