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MAIN ARTICLE

Hearing status in patients with rheumatoid arthritis

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Abstract

Objective: Rheumatoid arthritis is thought to induce conductive hearing loss and/or sensorineural hearing loss. This study evaluated the function of the middle ear and cochlea, and the related factors.

Methods: Pure tone audiometry, speech reception thresholds, speech discrimination scores, tympanometry, acoustic reflexes, and distortion product otoacoustic emissions were assessed in rheumatoid arthritis patients and healthy volunteers.

Results: Pure tone audiometry results revealed a higher bone conduction threshold in the rheumatoid arthritis group, but there was no significant difference when evaluated according to the sensorineural hearing loss definition. Distortion product otoacoustic emissions related prevalence of conductive or mixed hearing loss, tympanometry values, acoustic reflexes, and speech discrimination scores were not significantly different between the two groups. Sensorineural hearing loss was significantly more prevalent in patients who used azathioprine, cyclosporine and etanercept.

Conclusion: Higher bone conduction thresholds in some frequencies were detected in rheumatoid arthritis patients that were not clinically significant. Sensorineural hearing loss is significantly more prevalent in refractory rheumatoid arthritis patients.

Key words: Rheumatoid Arthritis; Hearing Loss; Audiometry; Cochlea

Introduction

Rheumatoid arthritis, the most prevalent chronic inflammatory form of arthritis, is characterised by symmetric peripheral polyarthritis that affects 0.5–1 per cent of the general population.[1] The first involved joints are typically small joints of the hands and feet, resulting in joint damage and physical disability.[2] As rheumatoid arthritis is a systemic disease, it may result in a variety of extra-articular manifestations, including auditory system disturbances.[3]

It is now more than 50 years since the first report of hearing loss in rheumatoid arthritis patients, by Copeman (1963), who termed it 'rheumatoid oto-arthritis'.[4] He reported on three patients with rheumatoid arthritis whose hearing was temporarily impaired when the severity of arthritis was exacerbated.[4] Since then, many studies have suggested a prevalence of 0 per cent to more than 48 per cent for sensorineural hearing loss (SNHL), and a prevalence of 0 per cent to 24 per cent for conductive hearing loss, in rheumatoid arthritis patients.[5–7]

The present study aimed to evaluate the hearing status of rheumatoid arthritis patients compared with healthy controls, and to assess the risk factors for hearing loss in these patients. A battery of tests including pure tone audiometry, tympanometry and distortion product otoacoustic emissions (OAEs) testing was used to investigate middle-ear and cochlear function more accurately.

Materials and methods

This prospective study was carried out from April to September 2015. The case group consisted of consecutive rheumatoid arthritis patients attending a rheumatology clinic, who were previously diagnosed by a rheumatologist (senior author) according to the American College of Rheumatology and European League Against Rheumatism 2010 criteria.[2] The control group consisted of healthy subjects (patients' friends or family members) who did not have any history of rheumatoid arthritis or any other connective tissue disorders. Participants were matched in terms of age and sex. All procedures performed in the study were in accordance with the 2008 Helsinki Declaration. Written informed consent was obtained from all individual participants included in the study.

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Patients with a history of congenital hearing impairment, anatomical abnormalities of the head and neck, severe head or ear trauma, chronic neurological disease, previous noise trauma or exposure to ototoxic agents (e.g. aminoglycosides such as streptomycin or gentamicin, excluding the drugs used for rheumatoid arthritis treatment), and recent upper respiratory tract infection were excluded.

A detailed history was obtained and a precise ENT examination was performed for all participants, with particular emphasis on hearing complaints, systemic comorbidities and drug history. All patients underwent laboratory tests including inflammation indices (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level), complete blood count and immunological parameters (rheumatoid factor and anti-cyclic citrullinated peptide) obtained during the 10 days prior to the hearing evaluation. The methotrexate cumulative dose was calculated by multiplying the methotrexate dose per week (in milligrams) by the duration of use (in weeks). As salicylates can cause transient reversible hearing impairment for up to 72 hours after discontinuation, the participants were asked to avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin for 3 days prior to audiological tests.[8]

All audiometric tests were performed by a single experienced audiologist who was blind to the study group participants. Audiological evaluations were performed in a sound-proof room, and involved assessment of speech reception thresholds, speech discrimination scores, pure tone audiometry, tympanometry, acoustic reflexes (using the Interacoustics® AZ26 clinical impedance audiometer) and distortion product OAEs testing (using the Neurosoft® Neuro-Audio device).

Pure tone audiometry was performed to assess hearing thresholds, using the Interacoustics AC40 clinical audiometer.[9] Air conduction thresholds were obtained at 250–8000 Hz and bone conduction thresholds at 250–4000 Hz. Sensorineural hearing loss was considered present when the average of bone conduction thresholds at successive frequencies of 500, 1000 and 2000 Hz exceeded 25 dB, and the air–bone gap was less than 10 dB. Conductive hearing loss was defined by an air–bone gap of more than 10 dB (in the aforementioned frequencies) when the average of air conduction thresholds was more than 25 dB and the average of bone conduction thresholds was within the normal range.[10] The presence of both SNHL and conductive hearing loss was considered as mixed hearing loss.

Tympanometry was performed to assess tympano-ossicular chain compliance and middle-ear pressure. The tympanograms were classified according to Jerger, as types A, As, Ad, B and C, in which A indicates a normal tympanogram.[11]

The acoustic reflex was measured via the contralateral stapedius reflex at 500, 1000, 2000 and 4000 Hz, in order to assess the changes in compliance created by the auditory stimulus-triggered stapedius contraction.

Distortion product OAEs testing was used to record the cochlear response at 1000, 1429, 2000, 2857, 4000, 5714 and 8000 Hz. The response was considered present when at least three successive frequencies were positive.

In order to assess the categorical variables, the chi-square test or Fisher's exact test was performed. Quantitative variables were compared using the *t*-test or Mann–Whitney U test. *P*-values of less than 0.05 were considered significant. The statistical analyses were performed using SPSS® software, version 22.

Results

A total of 82 individuals were included in this study. There were 42 rheumatoid arthritis patients (39 women, 3 men), with a mean age (± standard deviation (SD)) of 53.0 ± 7.5 years (range, 31–63 years). The mean disease duration was 8.6 ± 5.7 years (range, 1–20 years). The majority of the patients were middle-aged housewives. The control group consisted of 40 volunteers (36 women, 4 men), with a mean age (± SD) of 49.25 ± 10.4 years (range, 30–73 years). The differences between the case and the control groups in terms of sex, age and occupation were not significant. The underlying diseases (with the exception of rheumatoid arthritis) were also not significantly different between the two groups.

The most common drug combination for the treatment of rheumatoid arthritis patients was corticosteroid, methotrexate and hydroxychloroquine (40.5 per cent). Hydroxychloroquine was discontinued in eight patients (19 per cent) because of retinopathy. One patient had a rheumatoid nodule.

Pure tone audiometry revealed a significantly higher bone conduction threshold in the rheumatoid arthritis group in low frequencies and in the mean of 500–2000 Hz frequencies (Table I). However, when definitions of hearing loss were considered, there was no statistically significant difference between the two groups in terms of the prevalence of SNHL (11.9 per cent of the cases and 5 per cent of the controls), conductive hearing loss (7 per cent of the cases and 0 per cent of the controls) and mixed hearing loss

TABLE I
BONE CONDUCTION THRESHOLDS FOR VARIOUS FREQUENCIES IN CASES* AND CONTROLS†

Ear	Frequencies (Hz)	Group	BC threshold (mean ± SD)	*p*
Right	250–1000	Case	9.285 ± 7.158	0.016
		Control	4.750 ± 4.126	
	1000–4000	Case	16.349 ± 10.777	0.083
		Control	7.000 ± 6.226	
	500–2000	Case	10.714 ± 9.960	0.037
		Control	7.000 ± 5.445	
Left	250–1000	Case	9.047 ± 10.182	0.020
		Control	2.958 ± 5.501	
	1000–4000	Case	18.134 ± 12.699	0.054
		Control	6.208 ± 7.230	
	500–2000	Case	9.881 ± 12.679	0.016
		Control	7.750 ± 6.954	

*$n = 42$; †$n = 40$. BC = bone conduction; SD = standard deviation

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(2.4 per cent of the cases and 2.5 per cent of the controls).

In the rheumatoid arthritis group, there was a significant correlation between SNHL and use of azathioprine ($p = 0.006$), cyclosporine ($p = 0.004$) and etanercept ($p = 0.002$). However, there was no significant correlation between SNHL and age, sex, smoking status, vertigo, tinnitus, disease duration or retinopathy due to hydroxychloroquine consumption. The inflammatory markers (ESR and CRP), complete blood count, rheumatoid factor, anti-cyclic citrullinated peptide and methotrexate cumulative dose also showed no significant correlation with hearing loss.

Speech discrimination scores ranged from 80 to 100 per cent (means (± SDs) of 98.67 ± 4.01 per cent for the right ears and 99.07 ± 3.03 per cent for the left ears) in rheumatoid arthritis patients, and from 52 to 100 per cent (means (± SDs) of 99.60 ± 1.51 per cent for the right ears and 98.50 ± 7.68 per cent for the left ears) in controls. There was no statistically significant difference between the two groups.

Of the 84 ears tested with tympanometry in the rheumatoid arthritis group, 76 ears had type A tympanograms (1 As, 4 Ad), 1 ear had a type B tympanogram and 7 ears had type C tympanograms. Out of 80 control group ears, 78 had type A tympanograms (7 As) and 2 had type C tympanograms. There was no significant difference in tympanograms between the case and control groups.

Twenty-six of the 84 ears in the rheumatoid arthritis group, and 24 of the 80 ears in the control group, showed no acoustic reflex in the contralateral ear, revealing no significant difference between the two groups.

Distortion product OAEs testing was performed in 21 cases (42 ears) and 22 controls (44 ears). Twenty-two of 42 ears in the rheumatoid arthritis group and 21 of 44 ears in the control group had a positive response test result, with no significant difference between the two groups.

Discussion

Rheumatoid arthritis, the most common form of chronic arthritis, can result in various extra-articular manifestations.[3] As the inter-ossicular joints of the middle ear are believed to be true diarthrodial joints, with synovium and cartilage, they could theoretically be involved in the arthritis process, causing conductive hearing loss.[12,13] After Copeman reported conductive hearing loss in his patients, and proposed the possibility of its relationship with increased rheumatoid arthritis severity,[4] Ozcan *et al.* reported that the prevalence of conductive hearing loss and SNHL was about 24.1 per cent and 35.1 per cent, respectively, in rheumatoid arthritis patients.[6] However, our study showed a low prevalence (7.1 per cent) of conductive hearing loss in rheumatoid arthritis patients, with no significant difference when compared to the control group. The results of the present study are in line with studies by Goodwill *et al.*,[8] Ozturk *et al.*[7] and Murdin *et al.*,[14] who suggested that clinically significant conductive hearing loss was rare in rheumatoid arthritis patients.

Factors such as race, genetics, nutrition and environment may affect rheumatoid arthritis manifestations.[15,16] In our study, most of the patients had a relatively comfortable life. Treatment typically entailed a corticosteroid plus a usual disease-modifying anti-rheumatic drug such as methotrexate (88.0 per cent), hydroxychloroquine (95.2 per cent) or sulfasalazine (45.2 per cent). Azathioprine, cyclosporine and a biological disease-modifying anti-rheumatic drug (etanercept) were only required in 16.7 per cent, 2.4 per cent and 7.1 per cent of the patients, respectively. These data suggest a milder nature of rheumatoid arthritis in our patients, and therefore extra-articular manifestations were less likely to occur. In another study conducted in Iran on the prevalence of amyloid deposition in long-standing rheumatoid arthritis, a lower prevalence of this complication was observed compared to other countries (Mexico and Japan).[17]

Sensorineural hearing loss in rheumatoid arthritis could be induced by mechanisms that affect the inner ear, including vasculitis of 'vasa vasorum', and nerve neuritis, ototoxicity from the medications used to treat rheumatoid arthritis (e.g. NSAIDs, steroids, disease-modifying anti-rheumatic drugs), and autoimmune processes that destroy cochlear hair cells or immune complex deposition.[5,6,13,18–20] Some studies have shown a higher prevalence of hearing loss, especially of sensorineural type, in rheumatoid arthritis patients.[6–8,13,14,21] However, authors such as Rosenberg *et al.*[5] could not find any correlation between rheumatoid arthritis and hearing loss. The present study revealed that although there were statistically higher hearing thresholds in rheumatoid arthritis patients in some frequencies, they were not 'clinically' significant when the definition of hearing loss was applied.

Considering the correlation between hearing impairment and rheumatoid arthritis disease duration, Ozturk *et al.*[7] and Dikici *et al.*[13] believed that hearing impairment increased with an increase in the disease duration. When our patients were evaluated according to disease duration, we could not find any significant correlation.

Otoacoustic emissions testing records the mechanical sounds originating from the vibratory motion of the cochlear outer hair cells that transmit in a reverse direction to the external ear. Transient evoked OAEs (TEOAEs) testing has also been performed in rheumatoid arthritis patients. Murdin *et al.* stated that 18 per cent of rheumatoid arthritis patients had negative test results.[14] In addition, Dikici *et al.* reported a decrease in TEOAEs with age and with increased rheumatoid arthritis duration, and in men.[13]

Distortion product OAEs (DPOAEs) testing has proven effective in identifying individuals with SNHL.[22–25] Distortion product OAEs testing is specially designed to assess the function of the cochlea

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as a possible site for SNHL. The test depends on functional cochlear outer hair cells.[26,12] Distortion product OAEs are induced by the presentation of two pure tones (f1, f2) to the cochlea. These two frequencies make two various waves in the basilar membrane.[27] If the outer hair cells have normal function, a nonlinear interaction occurs where these two oscillations overlap, and a frequency distortion is induced.[28] Therefore, the presence of DPOAEs indicates normal outer hair cell functioning, and indirectly reveals the status of auditory sensitivity and hearing. To the best of our knowledge, this study was the first in which DPOAEs testing was performed to assess the cochlear function in rheumatoid arthritis patients. With the use of DPOAEs testing, we were able to assess cochlear responses in different frequencies that were positive in 52 per cent of rheumatoid arthritis group, with no significant difference as compared to the control group.

- **Conductive and sensorineural hearing loss (SNHL) have been suggested to accompany rheumatoid arthritis**
- **In this prospective study, 42 rheumatoid arthritis patients were compared to 40 controls using audiological tests**
- **Significantly higher bone conduction thresholds were revealed in some frequencies in the rheumatoid arthritis group**
- **However, no significant differences were found in the prevalence of SNHL (11.9 *vs* 5 per cent) or conductive hearing loss (7.1 *vs* 0 per cent) compared to controls**
- **Sensorineural hearing loss was significantly more prevalent in patients taking azathioprine, cyclosporine or etanercept**

Age-related changes in the cochlea may induce hearing loss, and the absence of acoustic reflexes and OAEs. As the mean age of our patients was 53 years, we attempted to match the case and the control groups by age in order to decrease its effect; the difference in age between the two groups was not significant.

Some medications could have considerable effects on hearing status. Salicylates, NSAIDs and antimalarial drugs have been shown to affect inner-ear cells. However, Rosenberg *et al.*[5] could not find any hearing impairment in their 39 rheumatoid arthritis patients, and Ozcan *et al.*[6] also stated that ototoxicity was not a common side effect for NSAIDs (except salicylate) and steroids in rheumatoid arthritis patients. Our survey revealed that patients using etanercept, azathioprine and cyclosporine had a higher chance of developing SNHL. The effect of these drugs on hearing status is not yet clear. There is a case report of progressive, reversible SNHL caused by azathioprine in an end-stage renal disease patient.[29] However, direct exposure of the cochlea to etanercept did not induce any cochleotoxicity in an animal study.[30] Similarly, cyclosporine has not been shown to induce SNHL.[31] Therefore, ototoxicity may not explain the higher prevalence of SNHL in patients taking these medications. Interestingly, although these three disease-modifying anti-rheumatic drugs have distinct mechanisms of action, all are prescribed for patients with severe diseases refractory to traditional disease-modifying anti-rheumatic drugs (methotrexate, hydroxychloroquine plus sulfasalazine). This may be the reason for differences in the results of various studies on the relationship between SNHL and rheumatoid arthritis, as the patients may experience different disease severities. However, we failed to find any correlation between hearing loss and inflammatory markers or anti-cyclic citrullinated peptide. Similar findings were observed by Dikici *et al.*[13]

There are various means to evaluate rheumatoid arthritis severity, and further investigations, including Disease Activity Score in 28 joints ('DAS-28') assessment, may be needed to detect any correlation.[32] The prevalence of conductive hearing loss and SNHL was low in our groups; a larger study may reveal differences between the two groups.

Conclusion

Higher bone conduction thresholds in some frequencies were detected in rheumatoid arthritis patients. However, there was no clinically significant difference in SNHL or conductive hearing loss in these patients compared to the control group (as evaluated using a battery of audiological tests including distortion product OAEs testing). Sensorineural hearing loss was significantly more prevalent in patients with refractory rheumatoid arthritis.

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