

ORIGINAL RESEARCH

Relationship between Disease Activity and Hearing Loss in Rheumatoid Arthritis Patients - A Case Control Study

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ABSTRACT

Objectives: Rheumatoid arthritis (RA) is well known to affect many different organ systems. Previous work suggests that this includes the auditory system. The objectives of this work are to evaluate the pattern of hearing impairment in patients with rheumatoid arthritis and to examine the possible associations between hearing impairment and related RA features especially disease activity.

Materials and methods: Thirty RA patients (mean age of 44.5 ± 9.9 years; female sex (90%)) and 17 healthy controls (mean age of 41.5 ± 9.1 years; female sex (76.4%)) were included in our study. The 2 groups were matched for age and sex ($p > 0.05$). Otoscopic examination was normal in all participants. No subject of the 2 groups has had any abnormalities at otoscopic examination. Hearing impairment was evaluated by pure tone audiometry and tympanometry including the static compliance, middle ear pressure, stapedial reflex threshold test. In all patients the clinical features, laboratory data, X-rays, disease activity index-DAS 28 were performed.

Results: Hearing loss was more prevalent in RA patients compared to healthy controls (56.7 vs 11.8%; $p = 0.005$). RA patients have conductive, sensorineural and mixed hearing loss in respectively 43.4, 3.3 and 10 % of cases. Association analysis between hearing characteristics and remission in RA patients shows that RA patients in remission have significantly lower mean hearing thresholds (12.8 ± 5.2 dB vs 18.8 ± 6.9 dB ; $p = 0.04$).

Conclusion: This study suggests that hearing loss risk is higher in RA patients and seems to be associated to disease duration. Hearing loss in RA was directly proportional to the disease activity index-DAS 28. Audiological evaluation must be performed periodically to identify possible audiological damage.

KEY WORDS: Rheumatoid arthritis, hearing loss, disease activity DAS 28

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory chronic disease of the joints. It is characterized by disease activity and bone destruction resulting in joint destruction, functional impairment, and increased mortality [1]. This chronic rheumatism is also a

chronic multisystem disease with a variety of systemic manifestations [2]. Previous work suggests that this includes the auditory system [3]. The nature and prevalence of hearing loss (HL) in rheumatoid arthritis (RA) remain debated [2,4]. Thus, each of the anatomical structures of the ear (internal, external and middle) has

been cited to be possibly affected by this chronic rheumatic disease [2,4,5]. The incudomalleolar and incudostapedial joints are true diarthroses. Those small synovial joints are located respectively between the malleus and the incus and the incus and the stapes. The 2 joint's function is to transfer vibrations between the ossicles in the middle ear, which is perceived as sound. In RA patients, the incudomalleolar and incudostapedial joints may be subject to the same rheumatic lesions as other articulations in the body [6,7]. In addition, Rheumatoid arthritis, by way of arteritis or neuropathy, could also cause sensorineural hearing loss or labyrinthine dysfunction [2,4,8]. Ototoxicity of RA medications used for the treatment of the disease has been also reported by previous data [2,9].

The objectives of this work are to evaluate the pattern of hearing impairment in patients with rheumatoid arthritis and also to examine the possible associations between hearing impairment and related RA features especially disease activity.

MATERIAL AND METHODS

Patients: Thirty consecutive adults' patients with RA aged between 18 and 55 years who suffered from the disease was recruited in this study between January and December 2012. RA patients were diagnosed by rheumatologists with reference to the American College of Rheumatology (ACR) classification criteria. Patients were followed by their rheumatologist and addressed for assessment as outpatients in El Ayachi hospital (public structure and referral hospital of Rheumatology in Morocco where hospitalizations and outpatient clinics are accessible for patients originary from different regions of our country). The choice of RA treatment was left to the discretion of the treating physicians. Exclusion criteria included patients at least one of the following conditions: diabetes, hypertension, dyslipidemia, Meniere's disease, a scarred or perforated tympanic membrane, history of otorrhoea, middle ear effusion, previous aural surgery, acoustic trauma, severe head injury. Seventeen healthy controls with any previously known diagnosis of a chronic condition or surgery of the middle ear (adhesive process, otosclerosis, perforation of the ear drum, cholesteatomatous otitis) were also excluded from the study. All patients agreed to enrollment in this study and signed written informed consent. The study was approved by the ethics review.

Patients' features and disease characteristics were assessed. Thus, the following parameters were collected at study entry: age, sex, comorbidity (other chronic diseases requiring long-term medical care), disease duration, patient's assessment of pain (on a visual analog scale), number of swollen and tender joints (both by 28 joint count), extra-articular manifestations, functional status evaluated by the Moroccan adapted version of Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level, IgM or IgA rheumatoid factor (RF) positivity (20 IU/ml and 7 units/ml, respectively), Anti-citrullinated protein/peptide antibodies (ACPA) positivity using second generation anti-CCP assay (CCP2) of ELISA. Concerning treatments, we recorded doses of oral corticosteroids and type of DMARDs received by patients. We assessed patient disease activity using the 28 joint disease activity score (DAS 28). Remission was defined by a DAS 28 score < 2.6 [8].

Audiologic tests: The studies were conducted in a soundproof chamber with calibration and equipment

maintained according to ANSI rules with a standard clinical audiometer. Two trained audiologists (I.R. and A.E) performed all studies, including pure-tone and speech audiometry (speech reception thresholds and word recognition scores), tympanometry, and acoustic reflex threshold test, on all cases and control subjects.

Frequencies at octave intervals from 250 to 8000 Hz were tested for air conduction and from 500 to 4000 Hz for bone conduction.

Hearing was considered abnormal if the thresholds were poorer than 25 dB hearing level at one or more test frequencies. Moreover, we used classification of the World Health Organization to classify the hearing impairment on basis of tone audiometry results: Mild hypoacusis: 27 to 40 dB, Moderate hypoacusis: 41 to 55 dB, Moderately severe hypoacusis: 56 to 70 dB, Severe hypoacusis: 71 to 90 dB and Profound hypoacusis <90 Db. Tympanometry, acoustic reflex thresholds were obtained using a Madsen Otoflex 100 immittance system. The tympanograms were classified according to Jerger as types A, As, Ad, B, and C. The acoustic reflex thresholds were considered normal if the stapedius muscle contraction occurred in an individual with normal hearing with acoustic stimulation between 80 to 100 dB HL for 500, 1000, and 2000-Hz test frequencies. The acoustic reflex decay test was defined as normal if the stapedius muscle contraction maintained at least 50% amplitude for greater than 5 seconds when exposed to pure-tone signals at 500 and 1,000 Hz at 10 dB sensation level above the acoustic reflex threshold.

HL was classified as sensorineural, conductive, or mixed. SNHL was defined as both air and bone conduction thresholds within 10 dB of each other and at least one test frequency poorer than 25 dB HL for air conduction. Conductive HL was defined as air conduction thresholds below normal for at least one frequency and bone conduction thresholds in the normal hearing range and at least 15 dB better than air conduction. Mixed HL was defined as both air and bone conduction below normal with an air-bone gap of at least 10 dB for at least one test frequency. Normal hearing with a conductive component was defined as air conduction thresholds within normal limits but bone conduction thresholds at least 15 dB better than air conduction.

Statistics : Descriptive statistics of the patients and disease characteristics were calculated. Outcome variables were dichotomized into qualitative variables: presence or absence of hearing loss. Results are presented using the median for continuous variables and frequency (percentage) for categorical variables. Respectively, the Wilcoxon rank sum test and Fisher exact test were used to perform between group comparisons. Univariate analysis tested most factors that were previously reported to be possibly related to hearing loss in RA. Multivariate logistic regression analyses were also conducted. A statistical significance level of $P < 0.05$ was used in all statistical tests performed. Analyses were performed using the SPSS program (version 13.0; SPSS Inc., Chicago, IL, USA)

RESULTS

Patients

Thirty RA patients (mean age of 44.5 ± 9.9 years; female sex (90%)) and 17 healthy controls (mean age of 41.5 ± 9.1 years; female sex (76.4%)) were included in our study. The 2 groups were matched for age and sex ($p > 0.05$). Otoloscopic examination was normal in all participants. The mean RA duration was 41 months (21,141). Anti-CCP was positive in 43.3% of patients. Eight RA patients were

in remission (DAS 28 < 2.6). Nineteen RA patients received a low dose of prednisone with a median dosage of 7.5 mg per day. Methotrexate (MTX) was the most frequently prescribed DMARD, being taken at a dose of 15 mg once a week by 56.7% of patients followed by Sulfasalazine and Chloroquine (16.7% for each of them). None of patients was on biologic therapy. Table 1 illustrates RA patients and healthy controls characteristics. Table 1 illustrates results.

Parameters	RA Patients N=30	Healthy controls N=17	P
Age (years)	44.5±9.95 *	41.05±9.12*	0.3
Female sex (%)	90	76.4	0.2
Disease duration (months)	41(21-141) **		
Anti-CCP positivity (%)	43.3		
DAS 28	4.2(2.5-5.9) **		
Disease activity			
Remission: DAS28 ≤2.6 %	28.6		
Low: 2.6 < DAS28 ≤3.2 %	3.5		
Moderate: 3.2 < DAS28 ≤5.1%	28.6		
High: DAS28 >5.1 %	39.3		
Treatment received			
Corticosteroids (%)	63.3		
Sulfasalazine (%)	16.7		
Methotrexate (%)	56.7		
Chloroquine (%)	16.7		

Table 1: RA Patients and Healthy controls characteristics

*values expressed as mean and standard deviation **Values expressed as median and quartiles ; RA : Rheumatoid Arthritis, DAS 28 : disease activity score : >5.1 = high disease activity ; 3.2 < ≤5.1 = moderate disease activity ; 2.6 < ≤3.2 = low disease activity ; ≤2.6 = remission

Compared to controls: RA patients have significantly more hypoacusia (36.7vs 5.9 %; p=0.03), vertigo (46.7vs 5.9%; p=0.004) and tinnitus (43.3vs 11.8 %; p=0.03). Although no one of healthy controls was complaining from earache and 3 RA patients have done, this difference was no significant. Figure 1 shows comparison of audiological symptoms between RA patients and healthy controls. Figure 1 illustrates results.

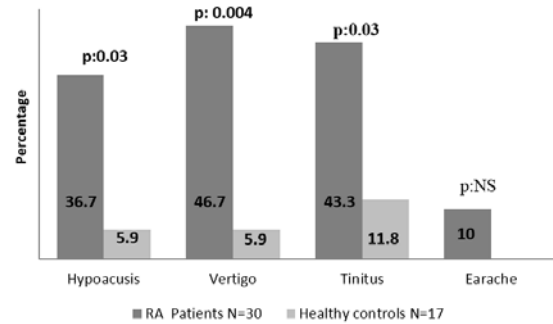


Figure 1: Comparison of audiological symptoms between RA patients and healthy controls (P significant if < 0.05 (Chi 2 test)).

Audiological tests

Compared to controls, RA patients exhibited statistically worse air conduction and higher bone conduction thresholds mostly at lowest frequencies in pure tone audiometry. Tables 2 and 3 illustrate results.

Test frequency (Hz)	Mean air conduction thresholds				
	RA patients		Healthy Control		p value
	Quartiles (dB)	Median (dB)	Quartiles (dB)	Median (dB)	
Right ear					
250	15-25	22.5	10-15	10	<0.001
500	15-25	20	10-15	10	0.001
1000	10-20	15	10-15	10	0.3
2000	10-20	15	10-15	10	0.2
4000	10-21.2	15	12.5-15	15	0.4
8000	10-31.25	15	15-20	15	0.9
Left ear					
250	13.75-25	20	10-15	10	0.009
500	15-21.25	17.5	10-15	15	0.002
1000	10-15	15	10-12.5	10	0.2
2000	10-20	15	10-15	10	0.3
4000	13.75-25	20	15-20	15	0.6
8000	14.12-30	22.5	17.5-27.5	20	0.8

Table 2 : Air conduction thresholds in pure tone audiometry (250- 8000 Hz) for RA patients and healthy controls p significant if ≤ 0.05 (Mann-Whitney test)

Frequency (Hz)	Mean bone conduction thresholds				
	RA patients		Healthy Control		p value
	Quartiles (dB)	Median(dB)	Quartiles (dB)	Median(dB)	
Right ear (dB)					
250	5-11.25	5	0-5	5	0.07
500	0-10	5	10	10	0.03
1000	0-6.25	5	5-10	10	0.01
2000	5-15	10	7.5-10	10	0.4
4000	5-15	10	5-10	5	0.6
Left ear (dB)					
250	5-11.25	5	0-5	5	0.07
500	5-11.25	5	10	10	0.1
1000	3.75-10	5	0-10	5	0.7
2000	5-15	10	10	10	0.5
4000	5-16.25	10	10-15	15	0.03

Table 3 : Bone conduction thresholds in pure tone audiometry (250- 4000 Hz) for RA patients and healthy control p significant if ≤ 0.05 (Mann-Whitney test)

The mean hearing thresholds was higher in RA patients than in healthy subjects (16.7dB vs 13 dB; p: 0.03). Air bone gap was higher in RA patients in comparison to healthy controls (8.3dB vs 3.3dB; p<0.001). Moreover, a pathological air bone gap (>10 dB) was more frequent in RA patients compared to healthy subjects (36.7 vs 5.9 %; p: 0.04). Even if tympanogram abnormalities were more frequent in RA patients compared to healthy controls (13.4 vs 5.9 %), this difference remains no significant (p >0.05); Figure 2 illustrates the results.

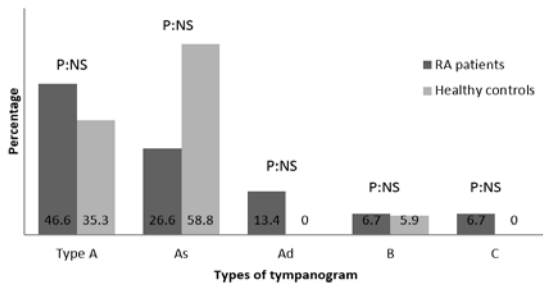


Figure 2: Types of tympanogram in RA patients and healthy controls

NS : no significant

Acoustic reflex was absent in 26.6% of RA patients and normal in all healthy controls (p =0.04).

Hearing loss was more prevalent in RA patients compared to healthy controls (56.7 vs 11.8%; p=0.005). RA patients have conductive, sensorineural and mixed hearing loss in respectively 43.4, 3.3 and 10 % of cases. Figure 3 illustrates the results.

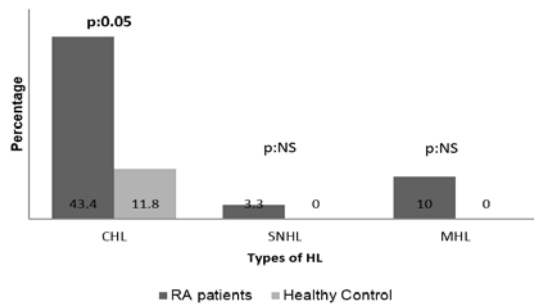


Figure 3 : types of hearing loss in RA patients and healthy controls

CHL : conductive hearing loss ; SNHL : sensorineural hearing loss ; MHL : mixed hearing loss ; NH : normal hearing
P significant if ≤ 0.05 (Chi2 test)

Association analysis between hearing characteristics and remission in RA patients shows that RA patients in remission have significantly lower mean hearing thresholds (12.8±5.2dB vs 18.8±6.9 dB ; p=0.04). All cases of absence of acoustic reflex were noted exclusively in RA patients without remission. No association was noted between remission in RA patients and air bone gap. Table4 illustrates the results.

Hearing Characteristics	RA Remission		p value
	Yes N=8	No N=22	
Mean hearing thresholds*	12.8± 5.2	18.8± 6.9	0.04
Absence of Acoustic reflex (%)**	0	40	0.06
Air bone gap*	8.7±3.1	9±4.9	0.9
Hearing loss (%)**	37.5	65	0.2

Table 4: Association analysis between hearing characteristics and remission in RA patients

*Values expressed as mean and standard deviation ; p significant if ≤0.05 (student t test) ** Values expressed as percentage ; p significant if ≤0.05 (Chi2 test)

DISCUSSION

Our study found a high prevalence of hearing loss in RA patients and showed that its nature could be conductive but also sensorineural, and mixte. In addition, hearing impairment seems to be associated RA activity. More abnormalities were observed in patients with active RA. RA patients have higher prevalence of hypoacusia, vertigo and tinnitus compared to healthy controls. Moreover, compared to controls, RA patients exhibited statistically worse air conduction thresholds than the control group mostly at lowest frequencies in pure tone audiometry (250, 500 Hz for air conduction and 500, 1000 Hz for bone conduction). In addition, air bone gap was higher in RA patients in comparison to healthy controls. In the same way, absence of the acoustic reflex was significantly more prevalent in RA patients compared to healthy subjects,

Those results are in concordance with literature. Low frequency air conduction threshold deteriorations and air bone gap increase were also observed by different investigators [5,10,11]. Presence of worse air conduction thresholds and larger air bone gaps at lower frequencies suggest subclinical middle ear involvement [4,12].

The prevalence of conductive hypoacusia was the most frequent in our patients. Nevertheless, this is much debated. The majority of data supports the view that the hearing loss type in RA patients could be conductive but also sensorineural as well as mixed [2,4].

Conductive hearing loss in RA may be related either to stiffness or to discontinuity of the ossicles in the middle ear. The incudomalleal and incudostapedial joints are true diarthroses. So, they may be involved by the disease process in RA, leading to stiffness of the ossicular system [4]. Physiopathology of SNHL seems to be complex and immune complex- mediated vasculitis of the inner ear. [2,5,13].

Exposure to ototoxic antirheumatic medications may play a role in hearing impairment in RA patients [1,14]. Drugs considered ototoxic, like methotrexate were used in majority of RA patients in our study. However, because of the small number of SNL cases, we haven't looked for relationship between methotrexate and hearing impairment in our study.

The presence of a mixed type of hearing loss (10%) suggested a multifocal involvement of the audiological system in RA [5, 10, 15].

The DAS disease activity score was higher in cases of RA with hypoacusia. Those results are consistent with some literature data [4,9,16,17,21]. Takatsu et al detected statistical significant correlations between the degree of hearing loss and the plasma concentrations of interleukin 6 and metalloproteinase [10]. Recently, Pascual-Ramos and al showed in a prospective study, on basis of an adjusted Cox proportional model, that cumulative disease activity predicted incidental hearing impairment [18,20]. Some limitations of this study should be pointed. First, we recognize that omitting high frequencies may be criticized and could possibly misjudge the inner ear involvement. High frequency audiometry, when is used as an investigation tool, is more sensitive in detecting inner ear insults than standard audiometry. Unfortunately, this method was not included in the design study because of technical considerations. In addition, our study is limited by its cross-sectional design, the small size of our sample and its heterogeneity. It would certainly more interesting if we have also integrated otoacoustic emission tests in the audiological tests for assessing better the inner ear.

Although those limitations, our study highlights the hearing involvement in RA patients. It is crucial for the clinician to be aware of this possible extra-articular involvement usually forgotten in RA patients. He should integrate audiological tests periodically in the disease management.

CONCLUSION

Our results suggest a dual effect of disease on both the middle and inner ears of patients with RA and showed the association between hearing loss and RA activity. Evaluation of audiometric tests should be integrated in RA assessment to detect and manage possible hearing impairment caused by the disease itself and or by therapeutic. Furthermore, patients must be informed by their physician of the risk of having auditory damage as a complication of the disease and should be also explained to patients.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals](#) of the [International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

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Declared none.

PATIENT CONSENT

Written informed consent was obtained from patients for publication of this study.

COMPETING INTERESTS

The authors declare no competing interests.

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