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ORIGINAL ARTICLE

Sensorineural Hearing Impairment and Subclinical Atherosclerosis in Rheumatoid Arthritis Patients Without Traditional Cardiovascular Risk Factors

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ABSTRACT

Objectives: This study aims to evaluate the association of hearing impairment with carotid intima-media thickness and subclinical atherosclerosis in rheumatoid arthritis (RA) patients.

Patients and methods: A total of 41 RA patients (2 males, 39 females; mean age 46.5±10.2 years; range 20 to 63 years) with no known traditional cardiovascular risk factors were included. Routine clinical and laboratory assessments for RA patients were performed. Pure tone air (250-8000 Hz) and bone conduction (250-6000 Hz) thresholds were obtained, tympanograms and impedance audiometry were conducted. Sensorineural hearing impairment was defined if the average thresholds were ≥25 decibels. Carotid intima-media thickness was assessed and classified with a cut-off point of 0.6 mm.

Results: Thirteen patients (31.7%) had normal audition, while 28 (68.3%) had hearing impairment. Of these, 22 had bilateral sensorineural hearing impairment. Four patients had conductive hearing impairment (right in three patients and left in one patient). Patients with sensorineural hearing impairment had increased carotid intima-media thickness in the media segment of carotid common artery compared to patients with normal hearing (right ear p=0.007; left ear p=0.075). Thickening of the carotid intima-media thickness was associated with sensorineural hearing impairment in RA patients.

Conclusion: Rheumatoid arthritis patients should be evaluated by carotid intima-media thickness as a possible contributing factor of hearing impairment in patients without cardiovascular risk factors.

Keywords: Atherosclerosis; hearing loss; rheumatoid arthritis.

Hearing impairment (HI) is recognized as an important cause of disability strongly associated with older age, noise exposure, and low income.[1,2] Diabetes mellitus, hypertension, and smoking are traditional cardiovascular risk factors considered as a contributing factor of HI among adults.[2-6] HI may be classified as conductive hearing impairment (CHI), sensorineural hearing impairment (SNHI), and mixed.

Rheumatoid arthritis (RA) patients have higher frequency of HI than healthy controls (42% vs. 15.9%).[7] RA is a disease characterized by

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inflammation of the synovial membrane of the diarthrodial joints, which include arthrodesis of the middle ear, (incudomalleolar and incudostapedial joints) causing CHI in up to 1.9% of the cases.[4] Extra-articular involvement may also affect the auditory system targeting the inner ear, causing SNHI in 22% to 43% of the patients.[4-10]

Hearing impairment in RA is generally underdiagnosed; symptoms are progressive and patients are not aware of the damage until it interferes with their usual activities.[5,6] Despite of the increasing number of research about this topic, there is no clear evidence indicating that RA per se might be a direct cause of HI since the physiopathology remains unclear.[4,7,11-13] There is no consensus about methods to perform, when to screen for HI in RA patients with audiometric and clinical methods, or usefulness of these methods.

Recognized causes of HI related to RA are disease activity, vasculitis, neuritis, immune-complex mediated antibodies directed against epitopes, and ototoxicity caused by medications.[14,15] The majority of the risk factors for SNHI reported in the literature are related to the cardiovascular system, as the inner ear may be vulnerable to circulatory alterations that can affect the labyrinthine artery.

Despite the probability that HI in RA patients may be associated with vascular damage, to our knowledge, previous research have not evaluated the association of cardiovascular damage with HI in RA patients.[5,6] Therefore, in this study, we aimed to evaluate the association of hearing impairment with carotid intima-media thickness and subclinical atherosclerosis in RA patients.

PATIENTS AND METHODS

This cross sectional study included 41 RA patients (2 males, 39 females; mean age 46.5±10.2 years; range 20 to 63 years), classified according to American College of Rheumatology criteria (1987).[16] attending to the Rheumatology Service of Hospital Civil "Dr. Juan I. Menchaca", Guadalajara, Jalisco, Mexico, between August 2013 and December 2013. Subjects who were former or current smokers, subjects with a history of cardiovascular disease, hypertension, diabetes mellitus type 2, thyroid disease, renal impairment, malignancy, hepatic disease or hyperlipidemia, or who were previously treated with high doses of steroids (>10 mg/day prednisone or equivalent, including intravenous administration) were excluded.

A structured questionnaire was applied to all subjects to gather demographic information, medical history, date of diagnosis, and current treatment. Disease activity was evaluated using the disease activity score in 28 joints (DAS28) with C-reactive protein (CRP).[17]

Venous blood samples were drawn and allowed to clot at room temperature and subsequently centrifuged at 1500 relative centrifugal force (Rotanta 460R, Andreas Hettich GmbH & Co. KG. Germany) for 10 minutes. The serum was stored at -70 °C until all the samples were obtained and further analyses were performed. Erythrocyte sedimentation rate (ESR) was measured using the Wintrobe method. The CRP and rheumatoid factor (RF) were measured by standard techniques (RANDOX Laboratories Limited, 55 Diamond Road, Crumlin, Country Antrim, BT29 4QY, UK). Anti-cyclic citrullinated peptide (CCP) antibody (U/mL) was measured by second generation enzyme-linked immunosorbent assay (Axis-Shield Diagnostics Ltd. Scotland).

Pure tone air (250-8000 Hz) and bone conduction (250-6000 Hz) thresholds were obtained using the audiometer AA-97B (Rion Co. Ltd., Tokyo, Japan) calibrated according to Japanese Industrial Standard T1201-2000. SNHI was considered when the auditory threshold was ≥25 dB in more than one of the frequencies between 250 and 8000 Hz (inclusively) and when the difference between air and bone conductive thresholds was <10 dB. CHI was considered when air conductive threshold was >20 dB and bone conductive ≤20 dB.

Hearing loss disability was defined when there was a decibel sum hearing loss of 100 dB or greater at frequencies of 500, 1000, 2000 and 3000 Hz in either ear, or of 50 dB or more in both ears at 4000 Hz.

Impedance audiometry was measured using an IA-AZ-7 model tympanometer (Middelfart, Denmark) calibrated to International Organization for Standardization standards. Tympanograms were classified according to Jerger as <A, As y C.

Carotid intima-media thickness (cIMT) was assessed according to the recommendations defined by the Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004-2006-2011).[18,19] by a single operator using a high-resolution B-mode ultrasound (PHILIPS, Saronno, Italy) with a 9-MHz transducer. Two segments from the common carotid artery (CCA), one from the carotid bifurcation, and two from the internal carotid artery were evaluated. Mean cIMT values were calculated for each segment. Patients were classified according to the cIMT with a cut-off point of 0.6 mm.

The study protocol was approved by the Institutional Review Board of "Hospital Civil Juan I. Menchaca", registered under the number 1068/10 and performed in accordance with the ethical standards laid down in the Declaration of Helsinki. A written informed consent was obtained from each patient.

Statistical analysis

Values are presented as mean ± standard deviation and percentages as appropriate. Between-group differences were estimated by independent-sample Student's t test. Chi-square test (or Fisher's exact test) was used to compare categorical variables. Spearman's correlation coefficient was calculated for cIMT and air conduction velocity. All data were analyzed using PASW version 18.0 software (SPSS Inc., Chicago, IL, USA), considering a two-tailed level of $p<0.05$ statistically significant.

RESULTS

Mean disease duration was 7.05 (7.37) years. Twelve patients (29.2%) had normal audition, while 29 (70.8%) had HI; of these, 28 (68.3%) had SHNI [22 (53.6%) had bilateral SNHI: 24 (58.5%) SNHI left and 26 (63.4%) SNHI right], three patients (7.3%) had right CHI, and one patient (2.4%) had left CHI. None of the patients had hearing loss disability. RF and anti-CCP were positive in 20 (48.5%) and 16 (39.0%) patients, respectively. Mean DAS28-CRP was 3.19±1.28 and DAS28-ESR was 4.10±1.26. Disease activity by DAS28-CRP was classified as severe in four patients (79.7%), moderate in 14 patients (34.1%), low in 12 patients (29.3%), and remission in 11 patients (26.8%). Clinical and serological features are shown in Table 1.

Patients with SNHI were older than patients with normal audition (49.68±8.8 vs. 39.54±9.8, p=0.002). No statistical differences were found between normal audition and SNHI groups,

Table 1. Hearing impairment according to clinical and demographic characteristics in rheumatoid arthritis patients

	Type of audition						
	Normal (n=13)			SNHI (n=28)			
All patients (n=41)	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			39.5±9.8			49.7±8.8	0.002
Female	13	100		26	92.9		0.323
Disease duration (years)			8.3±9.4			6.5±6.3	0.463
Rheumatoid factor (UI/L)			159.6±184.3			320.8±516.5	0.385
Rheumatoid factor positive	8	61.5		12	42.8		0.265
Anti-citrullinated cyclic peptide antibodies (UI/L)			130.1±98.1			308.0±358.9	0.163
Anti-citrullinated cyclic peptide positive	8	61.5		8	28.5		0.051
Erythrocyte sedimentation rate (mm/hour)			22.0±12.6			29.6±21.8	0.256
C-reactive protein (mg/L)			1.0±1.2			5.1±18.3	0.434
Disease activity index 28 joints-C-reactive protein							
Remission	3	23.1		8	26.6		0.437
Mild	6	46.2		6	21.4		
Moderate	3	23.1		11	39.3		
Severe	1	7.7		3	10.7		
Treatment							
Methotrexate	14	82.4		20	83.3		0.626
Sulfasalazine	9	52.9		10	41.7		0.537
Chloroquine	5	29.4		4	16.7		0.450
Azathioprine	0	0		2	8.3		0.502
Prednisone	1	5.9		2	8.3		0.212

SNHI: Sensorineural hearing impairment; SD: Standard deviation.

Table 2. Right carotid segments correlation with air conduction velocity in right ear

Right carotid segments	Air conduction velocity (Hz)						
	250	500	1000	2000	4000	6000	8000
Proximal CCA							
cc	-0.111	-0.067	-0.123	-0.042	-0.021	0.062	0.101
p	0.490	0.678	0.445	0.794	0.898	0.699	0.530
Media CCA							
cc	0.102	0.247	0.083	0.157	0.218	0.241	0.188
p	0.524	0.120	0.607	0.328	0.172	0.129	0.240
Distal CCA							
cc	0.078	0.120	0.039	0.246	0.370*	0.358*	0.350*
p	0.628	0.453	0.807	0.120	0.017	0.022	0.025
Bulb							
cc	0.068	0.144	0.022	0.063	0.092	0.107	0.056
p	0.671	0.369	0.890	0.694	0.568	0.507	0.728
Proximal ICA							
cc	-0.041	0.030	-0.039	0.050	0.025	0.040	0.013
p	0.797	0.853	0.807	0.755	0.878	0.804	0.935
Distal ICA							
cc	0.133	0.097	0.024	0.062	0.204	0.109	-0.016
p	0.406	0.545	0.881	0.702	0.200	0.496	0.920

Hz: Hertz; cc: Correlation coefficient; CCA: Carotid common artery; ICA: Internal carotid artery; * Statistical significance= p<0.05.

although higher titles of RF, anti-CCP, ESR and CRP were detected in the SHNI group. No statistical significant relationship was found between positivity for RF and anti-CCP between SNHI and normal hearing RA groups (data not shown).

Rheumatoid arthritis patients with right SNHI had thicker right media CCA compared to RA patients with normal audition (0.21±0.29 vs. 0.02±0.10, p=0.007); patients with left SHNI did not have difference in left media CCA compared to patients with normal audition (0.20±0.30 vs. 0.06±0.18, p=0.075). Other segments such as proximal and distal CCA, bulb, proximal and distal internal carotid artery in both sides did not show any significant differences according to right and left SHNI groups.

We detected a statistically significantly positive correlation between right distal CCA cIMT values

Table 3. Left carotid segments correlation with air conduction velocity in left ear

Left carotid segments	Air conduction velocity (Hz)						
	250	500	1000	2000	4000	6000	8000
Proximal CCA							
cc	0.045	0.096	-0.079	0.167	0.148	0.279	0.231
p	0.778	0.549	0.625	0.295	0.355	0.077	0.147
Media CCA							
cc	0.064	0.233	0.156	0.257	0.298	0.354*	0.325*
p	0.691	0.143	0.330	0.105	0.059	0.023	0.038
Distal CCA							
cc	0.132	0.170	0.014	0.232	0.195	0.249	0.268
p	0.411	0.287	0.929	0.145	0.221	0.116	0.090
Bulb							
cc	-0.132	-0.060	-0.177	0.057	-0.073	0.004	0.004
p	0.412	0.711	0.267	0.721	0.652	0.983	0.981
Proximal ICA							
cc	-0.047	-0.048	-0.224	-0.099	-0.107	-0.056	-0.055
p	0.771	0.764	0.159	0.536	0.504	0.726	0.732
Distal ICA							
cc	0.128	0.166	-0.110	0.033	0.002	0.063	0.013
p	0.425	0.301	0.495	0.835	0.988	0.695	0.938

Hz: Hertz; cc: Correlation coefficient; CCA: Carotid common artery; ICA: Internal carotid artery; * Statistical significance= p<0.05.

and abnormal audition at 4000 Hz [correlation coefficient (cc) 0.370, p=0.017), 6000 Hz (cc 0.358, p=0.022) and 8000 Hz (cc 0.350, p=0.025)] as shown in Table 2.

In addition, we found a positive correlation between medial CCA cIMT values and abnormal audition at 6000 Hz (cc 0.354, p=0.023) and 8000 Hz (cc 0.325, p=0.038) in the contralateral ear and artery, as shown in Table 3.

DISCUSSION

The pathogenesis of HI in RA has been a matter of debate for decades, and today, it is still poorly understood. Causes of HI have been described as multifactorial in the previous studies. SNHI seems to be the hearing damage most frequently found in RA patients, and it has been attributed to disease activity, older age and extra-articular involvement such as vasculitis.[8] In addition, majority of drugs used in the treatment of RA such as non-steroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs, given to patients with more active disease, have also been recognized as potential contributors to SNHI.[15,20-22] Thus, an association between disease activity and HI has not been not consistent.

Pascual-Ramos et al.[5] in a previous report demonstrated that 24% of 113 RA patients had HI. In a follow-up of their patients years later, they found in the adjusted Cox proportional model that cumulative DAS28-CRP was the only variable to predict incidental HI (odds ratio: 1.8, 95%; confidence interval: 1.1-2.7; p=0.01). Almost 13% of RA patients with short disease duration and low disease activity developed incidental HI within one year.[6] In 2005, Takatsu et al.[7] reported the frequency of SNHI in RA patients to be higher than normal controls (36.1% vs. 13.9%) and associated SNHI to ESR (p<0.05), plasma interleukin-6 (p<0.05), and plasma matrix metalloproteinase-3 (p<0.001) suggesting that systemic inflammatory process might trigger HI. On the other hand, Murdin et al.[4] did not find any relationship between hearing thresholds and markers of disease activity or other rheumatological parameters.

Cardiovascular disease in RA patients reduces life expectancy between six and seven years,[23] due to myocardial infarction, stroke, hypertension, and subclinical atherosclerosis.[19] In the last decade, RA has been recognized as a cardiovascular risk factor per se.[13] We have previously reported that cIMT correlates with levels of anti-CCP antibodies (r=0.513, p=0.001), CRP (r=0.799, p<0.001), tumor necrosis factor alpha (r=0.642, p=0.001), and interleukin-6 (r=0.751, p<0.001) in RA patients. In multiple regression analysis, cIMT was independently associated with CRP (p<0.001) and anti-CCP antibodies (p=0.03).[19] Gökmen et al.[24] have found that cIMT was positively correlated with the number of metabolic syndrome risk components in RA patients. They have shown positive correlations between cIMT and age, ESR, CRP, and systolic and diastolic blood pressures. On the other hand, cIMT has been associated with homocysteine levels in RA patients treated with methotrexate.[25] This increased risk is not exclusive to RA patients, increased cIMT has been reported in female patients with fibromyalgia.[26]

Hearing impairment may be associated with vascular damage in RA patients. Subclinical atherosclerosis may reduce the normal blood flow of brain circulation and this reduction may compromise the inner ear cells which are more sensitive to hypoxemic risk, leading to changes in the perception of high frequency sounds. Another possible explanation is that thickening of the intima-media carotid arteries may affect the inner ear blood flow, especially the labyrinthine artery, leading to SNHI by the same mechanism mainly at high frequencies. To our knowledge, we have shown for the first time that RA patients with SNHI had increased intima-media thickness in the carotid arteries. In a study of 381 consecutive patients who underwent coronary angiography for symptoms suggesting ischemic heart disease, Erkan et al.[27] found that the angiographic severity and extent of coronary artery disease are significantly and independently correlated with the degree of hearing loss. There was a statistically significant positive correlation between the degree of hearing loss at all frequencies analyzed (250, 500, 1,000, 2,000, 4,000 Hz) and the Gensini score (p<0.05 for all frequencies). Furthermore, in a case control study, Ciccone et al.[28] evaluated 29 patients with idiopathic sudden sensorineural hearing loss and 29 controls and showed that the two groups did not differ with regards to cIMT and other cardiovascular risk factors; however, flow-mediated dilation of

the brachial artery predisposed individuals to develop idiopathic sudden sensorineural hearing loss (p=0.03, odds ratio: 1.4).

There is evidence to suggest that hearing and vestibular function might be influenced by disease activity and autoimmune processes. RA patients may develop autoimmune inner-ear disease due to SNHI. There are some reports indicating that anti-tumor necrosis factor alpha agents (etanercept, adalimumab and infliximab) may offer additional treatment options for patients with autoimmune hearing loss.[20-22]

Hearing impairment in RA is a subclinical comorbid state. Since most of the patients are not aware of their HI and have no clinical complaints, it is important that physicians consider hearing damage in these patients.[2,3,14]

Despite of the increasing number of research on this topic, there is no clear evidence for the direct cause of HI, since the physiopathology remains unclear.[2,6,11] There is no consensus about audiometric evaluation methods and clinical screening in RA patients tested for HI. In this context, we are unable to differentiate the importance of RA itself and other comorbidities causing HI.

Our study has some limitations. Due to the cross sectional methodology of the study, we were unable to discriminate the impact of the variables across time in SNHI. And because of the small sample size, we might have missed a positive association of clinical and laboratorial variables with SNHI.

In conclusion, to our knowledge, we reported for the first time a positive association of subclinical atherosclerosis with SNHI in RA patients. As we have shown, auditory symptoms are common features associated with the disease. Follow-up appointments should be regarded as opportunities to enquire about hearing loss. Referral for screening and early treatment or rehabilitation increases the likelihood of a successful outcome. Further studies are required to elucidate the principal mechanism of SNHI, measure the labyrinthine artery by magnetic resonance imaging or computed angiotomography, and address cardiovascular risk factors and their impact in HI in RA patients.

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