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Early detection of cochlear hearing loss in rheumatoid arthritis patients: a cross-sectional study

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Abstract

Background: Rheumatoid arthritis (RA) is an inflammatory autoimmune disorder that has cardinal articular and peri-articular symptoms. Extra-articular manifestations (EAMs) are also reported among RA patients. In the current study, we assessed hearing function in 50 RA patients. An extensive audiological assessment including pure tone audiometry (PTA), extended high-frequency audiometry (EHFA), tympanometry, and acoustic reflex in addition to the oto-acoustic emission (OAEs) were done.

Results: Our data demonstrates that among the 50 participants with median disease duration of 8 years, about 80% had normal hearing using PTA and EHFA. However, 46% of them had—interestingly—demonstrated absent OAEs, suggesting early stages of cochlear hearing loss.

Conclusion: We conclude that rheumatoid arthritis can cause hearing impairment that can be early diagnosed by TEOAEs.

Keywords: Hearing loss, Rheumatoid arthritis

Background

RA is a chronic inflammatory autoimmune disorder that involves several body systems and dramatically affects patient's quality of life. It initially affects small body joints, but also extra-articular manifestations (EAMs) were reported which were believed to be mostly due to inflammatory processes. In a recent meta-analysis, which included 67 studies examining 742,246 RA patients and 211,592,925 healthy individuals, the global RA prevalence was estimated to be about 0.46% [1].

Among the reported EAMs in RA patients is the hearing impairment (HI). With the expected affection of patient's quality of life with HI, this had been generating a considerable interest to understand the pathophysiology,

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associations, and the possible way to manage it in RA patients in the last two decades [2].

All types of HI were reported in RA patients, sensorineural (SNHL), conductive (CHL) or mixed (MHL), where either middle ear, cochlea, or the auditory nerve are affected. SNHL is reported in the majority of the cases as a more common type of hearing impairment with prevalence ranging between 12 and 80%, affecting mostly the high frequencies. CHL or MHL were reported to be less common types of hearing loss in RA patients with prevalence of about 20 % [3].

Although the mechanism of how RA causes hearing loss is not well established, the inflammation affecting the middle ear and/or cochlea is suggested, as well as the auditory neuropathy and ototoxicity of the prescribed antirheumatic treatment [4]. Drugs commonly used in RA treatment as methotrexate and hydroxychloroquine were all documented to have ototoxic effect as a possible side effect [5, 6].

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Other suggested mechanisms include affection of external and\or middle ear by the fixation of rheumatoid ossicular joints or RA-associated destruction of joints and ligaments of auditory ossicles explaining As or B type tympanogram [3].

Different types of tympanograms can be detected in RA. As is found in ossicular chain fibrosis, Ad type is found in some cases possibly due to the inadequate perfusion of the ossicles due to vasculitis leading to dislocation. Sometimes type B is seen which recommend ossicular chain stiffness limiting its movement [7].

Different audiometry assessment tools were used in different studies ranging from PTA which is routinely used for detection of HI, to the EHFA that can more sensitively detect the earliest stages of hearing loss that include high frequencies before involvement of medium and lower frequencies in the more advanced cases of HI [3].

Oto-acoustic emissions are sounds emitted by human cochlea either in a spontaneous way or induced via acoustic stimuli. They are also reported to be affected in RA as an early stage of impaired hearing and can be a very early detection tool of hearing affection that can suggest changing the treatment protocols for a less ototoxic drugs especially in cases giving normal hearing with conventional hearing assessment [8].

The current paper is a preliminary attempt to validate the previous reports regarding the association of hearing loss with RA, in an Egyptian population from Delta region with their specific demographics regarding the life style, education, and occupation. It also calls into question the relation between the hearing impairment to RA activity and the duration among the participants using combination of different audiometric assessments.

Methods

This is a cross-sectional study carried out in the Audiology and Rheumatology clinics of Mansoura University Hospitals in the period between June and November 2021. Based on consecutive sampling method, 50 RA patients in the period of 6 months who met the 2010 criteria of American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) were included [9].

Patients between 16 and 50 years from both genders following a detailed clinical examination were included. Exclusion criteria include general systemic diseases like diabetes mellitus and hypertension. Local ear diseases that were excluded include congenital hearing loss, earache, otosclerosis, otitis media, ear trauma, acoustic trauma, otorrhea, Meniere's disease, occupational exposure to noise or administering ototoxic medications—excluding the RA drugs—patients with anatomic abnormalities of head and neck, previous skull or neck trauma, or middle ear operation.

The number of subjects who were recruited in the current study was determined using OpenEpi software [10], at alpha error of 0.05, power of 80%, confidence level of 95%, and the minimum sample was calculated to be 45.

As mentioned before, RA diagnosis was conducted based on 2010 ACR/EULAR criteria for RA. Rheumatoid factor (RF) as well as anti-cyclic citrullinated peptide (anti-CCP) antibodies were measured. In addition, disease activity score (DAS28) [11] was assessed. DAS in 28 Joints C-Reactive Protein (DAS28-CRP) was measured based on a count of 28 tender joints, 28 swollen joints, patient's general assessment, and laboratory value of CRP [12, 13].

In addition, clinical examination of ears was performed by audiologists which revealed normal tympanic membranes to the all 50 participants. Treatment history of RA patients was taken in details.

Audiological evaluation

Pure tone audiometry (PTA) was carried out in a soundtreated chamber to ensure not exceeding the maximum background noise levels according to the law of the European Economic Community. The PTA examination was conducted by using Madsen Itera 2 Clinical Audiometer (Natus, Denmark). The measurement was done according to ascending methodology (Hughson-Westlake, up 5, down 10 method). Air conduction thresholds were estimated for 250–8000 Hertz (Hz). Hearing threshold was computed as an average of 0.5–4 kHz in dBHL. Classification of audiograms was based on WHO criteria: normal hearing (≤25 dBHL), mild (26–40 dBHL), moderate (41–60 dBHL), severe (61–80 dBHL), and profound (≥81 dBHL) hearing loss. Hearing loss was defined as SNHL if air- and bone-conduction thresholds of >25 dBHL.

Extended high frequency audiometry (EHFA) was carried out also in a sound-proof room using Interacoustics AC 40 (Interacoustic, Assens, Denmark). Measurements were using an ascending-descending method, in 10-dB steps in 10,000, 12,000, 16,000, and 20,000 Hz. Means of high-frequency thresholds across test sessions among cases were 31 dB at 10,000 Hz, 38 dB at 12,000 Hz, 54 dB at 16,000 Hz, and 78 dB at 20,000 Hz.

Tympanometry was carried out by interacoustics AT 235 impedance audiometer (Interacoustic, Assens, Denmark). The patients were instructed to swallow eight to ten times to equalize the over or under pressure caused by tympanic membrane in their middle ears. Type A tympanogram was found in all cases.

Acoustic reflex (AR): ipsilateral AR was measured using interacoustics AT 235 impedance audiometer (Interacoustic, Assens, Denmark) at 500, 1000, 2000, and 4000

Hz. The intensity started from 70 to 80 dB HL up to 105 dB HL in 5 dB steps until an acoustic reflex threshold was obtained.

Oto-acoustic emissions (OAEs) were conducted utilizing Scout (Bio-logic, UK) TEOAES. They were not generated with a HI of 25–30 decibels. PASS indicated normal hair cell function and REFER indicated abnormal hair cell function with an enhanced risk of HI in future that recommends the early diagnostic abilities of OAE.

Statistical analysis

The data were analyzed by Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). For parametric data, Student's *T* test or the one-way analysis of variance (ANOVA) was used. For the non-parametric data, Mann-Whitney test (*U* test) or Kruskal-Wallis test was used. Chi-square test was used to examine the relationship between two qualitative variables. The reported *p* values were two-tailed and *p* <0.05 was considered significant.

Results

This work enrolled 50 RA cases with a mean age 40.1 \pm 5.3 age; the median of disease duration was 8 years (2–20). Patient's laboratory investigation, clinical assessment, and audiological measurements are demonstrated in Table 1.

In Table 2, correlation between audiological parameters and RF is shown; 23 cases (46%) were positive for RF and 27 cases (54%) were RF negative. To reveal if there is any correlation between the degree of hearing affection and RF among patients, PTA, EHFA, acoustic reflexes, and TEOAEs were all evaluated in relation to the RF results.

Twenty-one cases (91.3%) of RF-positive patients had normal PTA (<25 dBHL), and only two cases (8.7%) scored moderate (41–60 dBHL), compared to those with negative RF who showed that only 20 cases (74.1%) had normal PTA and seven cases (25.9%) scored mild PTA revealing no significant correlation between positive RF and hearing.

Among the 23 RF-positive cases, four cases had mild high-frequency SNHL (17.4%), while 11 of RF-negative cases (40.7%) had mild high-frequency SNHL. Also, in RF-positive cases, four cases (17.4%) had moderate SNHL, four cases (17.4%) had moderately severe SNHL, and two patients had severe high-frequency SNHL (8.7%). Concerning RF-negative cases, six patients (22.2%) had moderate SNHL, four (14.8%) had moderately severe SNHL, and four (14.8%) had severe SNHL. There is a significant correlation between positive RF and affected high frequency (p-value=0.042).

			Cases n=50	
Age		Mean \pm SD	40.1	±5.3
Duration		Median (mini- mum–maxi- mum)	8	2–20
RF	Negative	N, %	27	54%
	positive	N, %	23	46%
ACCP	Negative	N, %	12	24%
	positive	N, %	38	76%
DAS	Remission	N, %	28	56%
	Active	N, %	22	44%
PTA	Normal	N, %	41	82%
	Mild	N, %	7	14%
	Moderate	N, %	2	4%
EHFA	Normal	N, %	11	22%
	Mild	N, %	15	30%
	Moderate	N, %	10	20%
	Moderately severe	N, %	8	16%
	Severe	N, %	6	12%
Tympanometry	Туре А	N, %	50	100%
AR	Present	N, %	26	52%
	NR	N, %	24	48%
TEOAE	Pass	N, %	27	54%
	Refer	N, %	23	46%

RF rheumatoid factor, *ACCP* anti-cyclic citrullinated peptide, *DAS* disease activity score, *PTA* pure tone audiometry, *EHFA* extended high frequency audiometry, *AR* acoustic reflex, *TEOAEs* transient evoked oto-acoustic emission, *NR* no response, *SD* standard deviation

About 18 cases (78.3%) of RF-positive cases showed absent AR, while five had reflexes (21.7%), compared to six and 21 of RF-negative patients respectively, showing a significant association between being RF positive and absent AR (p-value < 0.001).

Regarding TEOAEs, 16 cases (69.6%) of RF-positive cases had refer in TEOAEs, while seven cases (30.4%) had pass TEOAEs. Seven cases (25.9%) of RF-negative cases had refer in TEOAEs, while 20 cases (74.1%) had pass. These data also show a highly significant association between RF positive and referred TEOAEs (p-value = 0.002).

Measurement of ACCP revealed that 38 were positive and 12 were negative ACCP. No significant correlation existed between ACCP results and PTA. Nine cases of negative ACCP had normal PTA having a percentage of 75% compared to 32 cases (84.2%) of positive ACCP patients. Three cases (25%) of negative ACCP had mild SNHL while four cases (10.5%) of positive ACCP patients had mild SNHL. Only two (5.3%) of positive ACCP cases had moderate SNHL (*p*-value= 0.373).

		RF				
		Negative n=27 N(%)		Positive n=23 N(%)		P value
PTA	Normal	20	74.1%	21	91.3%	0.007
	Mild	7	25.9%	0	0%	
	Moderate	0	0%	2	8.7%	
EHFA	Normal	2	7.4%	9	39.1%	0.042
	Mild	11	40.7%	4	17.4%	
	Moderate	6	22.2%	4	17.4%	
	Moderately severe	4	14.8%	4	17.4%	
	Severe	4	14.8%	2	8.7%	
Reflex	Present	21	77.8%	5	21.7%	< 0.001
	NR	6	22.2%	18	78.3%	
TEOAEs	Pass	20	74.1%	7	30.4%	0.002
	Refer	7	25.9%	16	69.6%	

Table 2 Correlation between audiological parameters and RF

RF rheumatoid factor, *ACCP* anti-cyclic citrullinated peptide, *DAS* disease activity score, *PTA* pure tone audiometry, *EHFA* extended high-frequency audiometry, *AR* acoustic reflex, *TEOAEs* transient evoked oto-acoustic emission, *NR* no response

Among the 38 ACCP-positive cases, eight cases had mild high-frequency SNHL (21.1%), while seven of ACCP-negative cases (58.3%) had mild high-frequency SNHL. Also, in ACCP-positive cases, 10 cases (26.3%) had moderate SNHL, four cases (10.5%) had moderately severe SNHL, and six patients had severe high-frequency SNHL (15.8%). Concerning ACCP-negative cases, four had moderately severe (33.3%). There is no significant correlation between positive ACCP and affected high frequency (*p*-value=0.097).

In ACCP-positive cases, 22 cases had absent reflex (57.9%), while 16 had reflexes (42.1%). However, only two cases of ACCP-negative cases had absent reflexes (16.7%) with 10 patients with having reflexes (83.3%), with significant association between positive ACCP and absent reflexes (p-value= 0.013).

A significant association between ACCP positive and refer in TEOAEs was also detected, where 55.3 % (21 cases) of ACCP-positive cases had refer in TEO-AEs, while only two cases showed TEOAEs refer among ACCP-negative cases (p-value=0.019). These results are shown in Table 3.

According to DAS-28, active cases were 22, while 28 cases were in remission.

Two of active DAS cases (9.1%) were significantly associated with higher proportion of moderate SNHL; also, 90.9% (20) of active DAS were normal hearers.

Among the 22 active DAS cases, 8 (36.4%) cases were normal hearers. Four had mild high-frequency SNHL (18.2%), while 11 of patients in remission (39.3%) had mild high-frequency SNHL. Also, in ACCP-positive cases, four cases (18.2%) had moderate SNHL, four cases (18.2%) had moderately severe SNHL, and two patients had severe high-frequency SNHL (9.1%). Concerning remission cases, four had moderately severe and severe SNHL (14.3%). There is no significant correlation between DAS and affected high frequencies (p-value=0.209).

Seventeen active cases had absent reflex (77.3%) while 21 cases (75%) of remission cases had reflexes.

A refer in TEOAEs was found in 68.2% (15) of active cases when compared to cases in remission as shown in Table 4.

To test the effect of disease duration on the audiological factors, correlation between the disease duration and previously measured parameters were measured. The data demonstrated that longer disease duration was significantly associated with affected high frequencies, absent reflex, and refer in TEOAEs (*p*-value= <0.001) in all. However, there was no association between RA duration and results of PTA as demonstrated in Table 5.

Discussion

Rheumatoid arthritis is a systemic autoimmune disease affecting less than 1% of the worldwide population [3]. It is associated with EAMs including ear. Middle ear, cochlea, and the auditory nerve are suspected sites of RA activity and hearing loss is a possible novel EAM of RA. SNHL has been reported as the most common hearing impairment in RA followed by CHL then MHL. Although retrocochlear involvement has been reported, most literature reports that cochlear pathology is the cause. The

		ACCP				p
		Negative n=12 N(%)		Positive n=38 N(%)		
PTA	Normal	9	75.0%	32	84.2%	0.373
	Mild	3	25.0%	4	10.5%	
	Moderate	0	0.0%	2	5.3%	
EHFA	Normal	1	8.3%	10	26.3%	0.097
	Mild	7	58.3%	8	21.1%	
	Moderate	0	0.0%	10	26.3%	
	Moderately severe	4	33.3%	4	10.5%	
	Severe	0	0.0%	6	15.8%	
Reflex	Present	10	83.3%	83.3%	42.1%	0.013
	NR	2	16.7%	16.7%	57.9%	
TEOAEs	Pass	10	83.3%	17	44.7%	0.019
	Refer	2	16.7%	21	55.3%	

Table 3 Correlation between audiological parameters and ACCP

RF rheumatoid factor, *ACCP* anti-cyclic citrullinated peptide, *DAS* disease activity score, *PTA* pure tone audiometry, *EHFA* extended high-frequency audiometry, *AR* acoustic reflex, *TEOAEs* transient evoked oto-acoustic emission, *NR* no response

Table 4 Correlation between audiological parameters and DAS

		DAS			р	
		Remission n=28 N(%)		Active n=22 N(%)		
PTA	Normal	21	75%	20	90.9%	0.010
	Mild	7	25%	0	0%	
	Moderate	0	0%	2	9.1%	
EHFA	Normal	3	10.7%	8	36.4%	0.209
	Mild	11	39.3%	4	18.2%	
	Moderate	6	21.4%	4	18.2%	
	Moderate to severe	4	14.3%	4	18.2%	
	Severe	4	14.3%	2	9.1%	
Reflex	Present	21	75%	5	22.7%	< 0.001
	NR	7	25%	17	77.3%	
TEOAEs	Pass	20	71.4%	7	31.8%	0.005
	Refer	8	28.6%	15	68.2%	

RF rheumatoid factor, ACCP anti-cyclic citrullinated peptide, DAS disease activity score, PTA pure tone audiometry, EHFA extended high-frequency audiometry, AR acoustic reflex, TEOAEs transient evoked oto-acoustic emission, NR no response

structure of the inner ear is disturbed by vasculitis, neuritis, and the ototoxic drugs used in treatment.

However, the results of previous studies evaluating the link between RA and hearing impairment are confusing. Therefore, we performed this research work to provide an update on the clinical aspect of hearing impairment in RA.

In the current study, the correlation between PTA, EHFA, tympanometry, AR, and OAEs in relation to RF,

ACCP, DAS score, and disease duration was studied and addressed. SNHL was the dominant type of hearing loss. OAEs which are sounds found in the external auditory arising from the vibratory motion of the outer hair cells and corresponding closely to the physiological state of outer hair cells of the cochlea were of very high value in early investigating SNHL in our patients.

About 80% of our patients had normal hearing using PTA and EHFA while 46% of them
 Table 5
 Correlation
 between
 audiological
 parameters
 and

 disease duration

		Duration Median (minimum– maximum)	p
PTA	Normal	8 (2–20)	0.112
	Mild	3 (3–4)	
	Moderate	9 (9–9)	
EHFA	Normal	6 (2–13)	<0.001
	Mild	16 (7–20)	
	Moderate	8 (6–9)	
	Moderate to severe	16 (7–20)	
	Severe	16 (7–20)	
Acoustic reflex	Present	4 (2–10)	<0.001
	NR	11 (7–20)	
TEOAEs	Pass	4 (2–13)	<0.001
	Refer	10 (2–20)	

RF rheumatoid factor, *ACCP* anti-cyclic citrullinated peptide, *PTA* pure tone audiometry, *EHFA* extended high-frequency audiometry, *AR* acoustic reflex, *TEOAEs* transient evoked oto-acoustic emission, *NR* no response

had—interestingly—demonstrated absent OAEs, suggesting early stages of cochlear hearing loss. Affection of TEOAEs in this study gives as a good tool to early detect SNHL in rheumatoid arthritis patients regardless of pure tone results. Also, it gives us an idea about the pathophysiology of SNHL in rheumatoid arthritis patients by highlighting the outer hair cell affection in these patients.

As mentioned in Table 2, a significant correlation existed between RF and PTA or EHFA in agreement with Munjal et al. [14] and a non-significant correlation between RF and HI was found in accordance with Gamala et al. [15] and Ahmadzadeh et al. [16]. A significant association existed between positive RF and absent AR, referred TEOAEs when compared to negative RF.

Concerning ACCP results, we found no significant correlation between ACCP and PTA and EHFA in agreement with Gamala et al. [15], Ahmadzadeh et al. [16], and Murdin et al. [17], while Lobo et al. [8], Pascual-Ramos et al. [18], and Munjal et al. [14] reported a significant association between RF and PTA thresholds and EHFA thresholds. Positive ACCP was significantly associated with higher proportion of absent AR and referred TEO-AEs when compared to negative ACCP.

DAS results mentioned in Table 4 are in a significant relationship with abnormal PTA, absent acoustic reflex, and referred TEOAEs when compared to remission in agreement with Yildirim et al. [19]. In contrast, other researches did not report a relationship between HI and disease activity as Murdin et al. [17], Lasso de la Vega et al. [13], and Lobo et al. [8].

Also, we found that longer RA duration was significantly linked to abnormal high frequencies, absent acoustic reflex, and referred TEOAEs in agreement with Nasution and Haryuna [20] and Öztürk et al. [21] who showed that the longer the RA duration, the more advanced the stage of disease [7, 8, 22, 23] (Table 5).

Cochlear impairment among RA patients is confirmed by the findings of our study. An inverse correlation between disease duration and TEOAE amplitude were found which indicates that inner ear injury is dependent upon chronic cochlear damage associated with RA. Since inner ear microcirculation is involved in RA-related systemic vascular impairment, cochlear function assessment utilizing TEOAEs might represent an easy and non-invasive novel approach for RA staging, in association with traditional rheumatological parameters [24].

In the current study, significant associations existed between disease duration and high-frequency thresholds. In a patient with longer RA duration, the pathogenetic process of RA itself together with administration of ototoxic medications might result in a damage of the inner ear. In contrast, Lasso de la Vega et al. [13] did not report any association between disease duration and HI among RA patients.

To the best of our knowledge, this study is the first to detect an association between RF, AR, and TEOAEs and also between ACCP, AR, and TEOAEs. A significant association existed between positive RF and absent AR, referred TEOAEs when compared to negative RF. Positive ACCP was significantly associated with higher proportion of absent AR, referred TEOAEs when compared to negative ACCP.

Limitations

As mentioned before, SNHL in RA patients may be due to the pathology of the disease itself or due to ototoxicity of anti-rheumatic drugs. Although retrocochlear affection has been reported, the majority of studies reported that cochlear pathology was the cause. The inner ear structure is impaired by vasculitis, neuritis. This study did not prove the exact etiology of HI among RA patients.

Thus, further research must be performed to evaluate the role of different pathologies occurring in RA and causing Hl and also the impact of medications utilized in RA treatment.

Conclusion

RA can result in hearing loss. We suggest that the etiology of hearing loss in our study is due to different processes occurring in RA including auditory neuropathy and damage of cochlear hair cells. We think that OAEs should be added as a valuable tool in evaluating rheumatoid arthritis patients which may guide rheumatologists to change drugs prescribed for such patients or to try to delay expected hearing loss as can as possible in a trial to avoid deterioration in the patient's life style. We recommend regular assessment of hearing to improve patient's quality of life.

Abbreviations

RA: Rheumatoid arthritis; PTA: Pure tone audiometry; EHFA: Extended high-frequency audiometry; OAEs: Oto-acoustic emissions; TEOAEs: Transient evoked oto-acoustic emissions; EAMs: Extra-auditory manifestations; HI: Hearing impairment; SNHL: Sensorineural hearing loss; CHL: Conductive hearing loss; MHL: Mixed hearing loss; ACR-EULAR: American College of Rheumatology and European League Against Rheumatism; ACCP: Anti-cyclic citrullinated peptide; RF: Rheumatoid factor; DAS28-CRP: DAS in 28 Joints C-Reactive Protein; AR: Acoustic reflex.

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Authors' contributions

OE contributed to the idea, supervision, and analyses of the results. NE contributed to the supervision and participated in the data collection and analysis of the results. SE contributed to data analysis, writing, and critical revision of the draft. EF contributed to the analysis and writing. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

The datasets are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The approval of the Mansoura Institutional Research Board (IRB) was taken reference no. (R.21.01.1108) and informed consent from all participants was obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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