Peripheral and central auditory pathways function with rheumatoid arthritis

Aims: We aimed to determine auditory pathways functions with rheumatoid arthritis (RA). **Materials & Methods:** Included were 46 adult females. They underwent audiometry, transient evoked otoacoustic emissions (TEOAEs) and brainstem-auditory response (ABR). **Results:** Hearing losses were reported in 60.87% ears. Compared to controls, TEOAE at 3.0–4.0 kHz were lower in 39.13% ears. ABR showed prolonged waves I and III–V latencies. Prolonged wave I and III–V and I–V latencies were observed in 45.65, 39.13 and 17.39% ears. Significant associations were identified between duration of RA and hearing thresholds, waves I and III and III–V and I–V latencies and TEOAEs amplitudes at 4 kHz. **Conclusion:** Chronic RA causes pathologies of the auditory nerve, cochlea and auditory pathway within the brainstem.

Keywords: auditory-brainstem response • auditory function • cochlea • rheumatoid arthritis • transient evoked otoacousttic emissions

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Rheumatoid arthritis (RA) is the most common autoimmune disease. RA is a chronic inflammatory multisystem connective tissue disorder. Disseminated erosive arthropathy, which include cartilage damage and bone erosions and subsequent changes in joint integrity as a result of synovial inflammation, is the hallmark of the disease [1]. The approximated prevalence of RA in white populations of northern European and North American ranges from 0.5 to 1% [2] and even up to 3% in adult population with a usual age of onset is from 35–45 years [3] and a mean annual incidence ranges from 0.02 to 0.05% [2], whereas reports from Africa note a rising incidence, for example the prevalence of RA is approximately 0.3% in Egyptian population [4]. In addition to joints, RA also involves a variety of systemic or extra-articular inflammatory manifestations (e.g., pericardial effusion, pleuritis, major cutaneous vasculitis, subcutaneous nodes, Felty's syndrome [association with neutropenia and splenomegaly], polyneuropathy, amyloidotic nephropathy, glomerulonephritis, ophthalmological manifestations as episcleritis, kera-toconjunctivitis sicca, endophthalmitis and glaucoma which may lead to blindness and other types of vasculitis) [5].

Several studies have shown that hearing impairment is one of the extra-articular manifestations of RA. Conductive (CHL), sensorineural (SNHL) [5–14] and mixed [15,16] (MHL) hearing losses are common findings with RA. Some investigators suggested that most of the hearing loss in RA is conductive in nature (CHL) due to impairment of the middle ear transducer mechanism. This is caused by involvement of the incudo-malleolar and incudo-stapedial joints (the middle ear ossicular diarthroidal joints, which are synovial joints) by inflammation followed by increased stiffness in the tympanoossicular system, ankylosis or decreased mobility or fixation [6,7,9]. It has also been suggested that CHL may be caused by increased laxity or hyperlassitude of the transduction mechanism or discontinuity in the ossicular chain of the conducting system caused by increased collagenolysis with RA or discontinuity of the ossicles [17]. Others reported that the significantly greater hearing loss in RA patients

was SNHL as a result of auditory nerve, cochlear (or inner ear) and auditory pathway pathologies caused by the immune-mediated process of RA which results in vasculitis or arteritis of the vasa nervosum of the auditory nerve [10,11,13,14]. However, ototoxicity by some anti-rheumatic drugs (e.g., salicylates, nonsteroidal anti-inflammatory drugs [NSAIDs], chloroquine and methotrexate) beside damage of the inner ear structures has been suggested by some authors as a cause for SNHL in RA patients [18]. In fact, the frequency of hearing impairment with RA varies greatly in different populations, the type and nature of hearing disorder in patients with RA is still a subject of debate and the exact pathophysiology of auditory dysfunction with RA is still incompletely delineated.

This study aimed to determine the peripheral, cochlear and central auditory pathway functions in a group of patients with RA with no clinical auditory complaints.

Patients & methods
Patients
This comparative case-control study included 46 females (≥20–<55 years old) with RA [19]. Patients were recruited from the Rheumatology Outpatients' Clinic of Assiut University Hospital, Assiut, Egypt. Forty age- (range = 20–55, mean = 42.50 ±3.60 years) and sex- (male = 0, female = 40) matched healthy subjects recruited from the general population served as control subjects for comparison. Control subjects were also matched for socioeconomic and educational levels. Excluded were subjects with history of ear disease (e.g., a scarred or perforated tympanic membrane, chronic otitis media, Meniere's disease, otorrhea, middle ear effusion, severe head injury, previous aural surgery), other systemic or metabolic diseases associated with hearing loss (e.g., renal insufficiency, gout, diabetes mellitus, hypertension, hypercholesterolemia/dyslipidemia, hypothyroidism), clinical evidence of postural hypotension, reported exposure to unsafe noise, previous use of ototoxic drugs (other than those used for treatment of RA) and family history of hearing loss.

The study protocol was accepted by the regional Ethics Committee. Detailed information on the study was given to all participants and all gave their written consent to attend the study.

Methods
Demographic, clinical & laboratory characteristics
All participants underwent complete rheumatologic, medical, neurologic and audiologic evaluations. The clinical characteristics of the patients were recorded by joint pain assessment using visual analogue scale (VAS) [20], morning stiffness, number of tender joints

(Richie index) [21], number of arthritic joints, presence of rheumatoid nodules, functional capacity assessed according to ACR revised criteria for the classification of global functional status in RA [22]. Disease severity was assessed by the ARA X-ray staging, as well as by RA seropositivity and presence of extra-articular manifestations [23]. Radiological grading were performed and staged according to Larsen index (0–4) where grade 0 is normal and grade 4 is mutilating abnormality [24]. Routine hematological tests were done and included erythrocytic sedimentation rate (ESR), CRP (C-reactive protein), complete blood count (CBC), blood sugar (fasting and postprandial), renal and liver functions, lipogram (serum total cholesterol [TC], triglycerides [TG], low density lipoprotein cholesterol [LDL-c], high density lipoprotein cholesterol [HDL-c]) and uric acid. Routine serology included rheumatoid factor (RF) which was determined by latex agglutination test, RF titer of 1:80 was considered significant.

Basic audiological evaluation
All participants underwent basic audiological evaluation that included: initial otoscopic examination, pure tone air and bone conduction audiometry (PTA), speech audiometry, tympanometry and stapedius reflex. PTA is a subjective key hearing test used to identify hearing threshold levels of an individual, enabling determination of the degree, type and configuration of a hearing loss [25]. Air conduction hearing threshold levels for octave frequency between 250–8000 Hz (mid or low frequencies) and bone conduction hearing threshold for frequencies between 250–4000 Hz, were done using dual channel clinical audiometer Madsen OB822 (Assens, Denmark). The type of hearing loss (CHL versus SNHL) can also be identified via the air–bone gap. Hearing thresholds were determined in decibel hearing level (dB HL). The examined ears were defined as normal if no absolute threshold level >20 dB was measured over the whole frequency range. Threshold shifts in PTA were considered to be significant if they showed at least 10 dB (decibel) change in more than two consecutive frequencies, or if a threshold greater than 20 dB was observed in any audiometric range. Hearing loss was calculated for each ear separately as the amount of threshold shifts above the standard audiometric zero. Grading of hearing impairment was adopted according to Northern and Downs [26] into: mild, moderate, moderately severe and severe impairment, which is defined as average threshold between 25–40 dB, 41–55 dB, 56–70 dB and 71–90 dB, respectively.

As communication through speech is the major function of hearing, speech audiometry was done in which the clinician presents the speech stimuli through

the microphone of the audiometer [27]. It is possible for two patients to have the same audiogram but have very different abilities to use the information they receive. Education and culture are important variables which may affect the results of this test. Speech Audiometry includes Speech Reception Threshold (SRT) and Speech Discrimination. SRT is the intensity at which simple speech material (presented in live voice), usually spondees, can be detected ≥50% of the time. Spondees are word with two syllables (bisyllables) that have equal stress on each of the syllables, for example, fruitcake, meatball, childcare, *etc*. Monosyllables (i.e., single syllable words) are used to test speech discrimination. When the patient has CHL, he/she is still able to discriminate speech clearly (≥90% of the time) if loud voice is used. However, if the patient has SNHL, the clarity of speech is affected so that no matter how loud the speech is heard [27].

Tympanometry is an objective test of middle-ear function, mobility of the ear drum (tympanic membrane) and the bone conduction by creating variations of air pressure in the ear canal. Tympanometry is not a hearing test, but rather a measure of energy transmission through the middle ear and the results of this test should always be viewed in conjunction with pure tone audiometry [6]. Low frequency tympanometry (+200 top – 400 dapa) and the stapedius reflex were done using Middle Ear Analyzer Interacoustics (Az26, Assens, Denmark). Most middle ear problems result in stiffening of the middle ear. A normal tympanogram is labeled as Type A, while abnormal tympanogram is labeled as Type B or C.

The stapedius reflex is an involuntary muscle contraction that occurs in the middle ear in response to high sound intensities; while its activation for quieter sounds indicates ear dysfunction at any of the following levels: ossicular chain (malleus, incus and stapes), the cochlea (organ of hearing), the auditory nerve, brain stem, facial nerve and other components [28].

Transient evoked otoacoustic emissions (TEOAEs)

Otoacoustic emission (OAE) studies are more sensitive and objective measures of assessing cochlear function in different clinical diseases compared with PTA. TEOAEs result from transient spontaneous movement of the outer hair cells (OHCs) of the Organ of Corti (which are responsible for the cochlear sound amplification) in response to acoustic stimuli [29]. TEOAEs were recorded using a commercially available system (ILO88, Otodynamic Ltd, Hatfield, UK, v.4.2) as described before [14]. TEOAEs 'global and band response levels (1.0, 1.4, 2.0, 2.8, 4.0 kHz) were compared between patients and controls. TEOAEs

values were considered abnormal when the levels were two standard deviations (SD) below the mean of the controls.

Auditory-brainstem response recording

Auditory-brainstem response (ABR) represents the signal averaging computer elimination of electroencephalographic activities (EEG) which are less contributed by the auditory nerve and auditory brainstem. In other words, ABR average out the 99% of the EEG that is not auditory generated and produces an auditory-only record. The procedure is efficient, reliable and inexpensive. ABR recording was done using Nicolet Spirit OS/2 version 1. ABR was performed using alternating clicks at 0.1 seconds, time window was 10 ms and filter settings were 150–3000 Hz. The stimuli were delivered at 90 dBHL with repetition rate of 11.1–51.1 pulse/second. Each response reflected an average of 1500 stimuli presentations. The absolute latencies of waves I, III and V and interpeak latencies (IPLs) of I–III, III–V and I–V were recorded from both ears.

Conventional ABR evaluation uses a repetition rate of 60–80 stimuli/s but rapid stimulus rate is not a routine part of ABR test protocol internationally. It has been reported that ABR morphology is a function of stimulus rate. High repetition rate increases the sensitivity of the ABR in the detection of small lesions within the auditory pathway particularly wave V and I–V IPLs [30,31]. Burkard and Sims [32] showed that latency increase was nearly linear with stimulus rate increases between 25 and 75 stimuli *per se*cond and was nonlinear with rates exceeding 75/s.

Statistical analysis

Calculations were performed using SPSS, version 12.0. Data were presented as mean ±SD when normally distributed and mean (quartiles) when not normally distributed (TEAOEs). The Kolmogorov–Simirnov test was used to test distributional characteristics. Independent two-sided Student's *t*-test was used for comparison of the means of normally distributed measures and Mann-Whitney *U*-test was used for comparison of the means when not normally distributed (TEAOEs). Pearson's r was used to assess correlations for normally distributed data while Spearman's methods were used for non-normally distributed data. For all tests, values of $p < 0.05$ were considered statistically significant. To determine the relationship between audiologic and demographic variables, a multivariate analysis (Odd's ratio [OR] and 95% confidence interval [95% CI]) was undertaken using values of audiologic testing (hearing thresholds at 8000 Hz, I–V IPLs of ABR at high repetition rate frequencies and TEOAEs levels at 4 kHz) as dependent variables. In the first step, bivari-

Table 1. Demographic, clinical and laboratory data of the studied rheumatoid arthritis patients.	
Variable	**Data**
Age at presentation (years)	≥20–<55 (46.64 ±9.92)
Gender (M/F)	0/46
Duration of illness (years)	2½–25 (8.99 ±3.20)
Morning stiffness (min)	15–240 (80.38 ±42.52)
Number of active joints	0–25 (5.84 ±3.32)
RAI	0–25 (12.35 ±8.63)
Pain scale (VAS)	2–9 (5.23 ±2.22)
Functional capacity (range: 1–4)	1.55 ±0.79
X-ray grading (G0–4)	
G1	10 (21.74%)
G2	26 (56.52%)
G3	8 (17.39%)
G4	2 (4.35%)
SN	8 (17.39%)
Laboratory findings	
C-reactive protein	
Positive	30 (65.22%)
Negative	16 (34.78%)
RF	
Positive	20 (43.48%)
Negative	26 (56.52%)
ESR	
High	17 (36.96%)
Normal	29 (63.04%)
Treatment	
MTX and NSAIDs	20 (43.48%)
Steroids	3 (6.52%)
NSAIDs	17 (36.96%)
Colchicines	1 (2.17%)
MTX, hydroquinone	3 (6.52%)
MTX, hydroquinone and steroids	2 (4.35%)

Data are expressed as mean ±SD (standard deviation) and number of patients and their percentage.
ESR: Erythrocytic sedimentation rate; MTX: Methotrexate; NSAID: Nonsteroidal anti-inflammatory drug; RAI: Richie articular index; RF: Rheumatoid factor; SN: Subcutaneous nodule;

tivariate analysis. For all tests, values of $p < 0.05$ were considered statistically significant.

Results
Included were 46 females with RA with mean age of 46.64 ±9.92 years and duration of illness of 8.99 ±3.20 years. Table 1 showed the demographic and clinical characteristics of the studied patients. Apart from the presence of subcutaneous rheumatoid nodules (17.39%, n = 8), none of the patients had obvious extra-articular manifestations.

Pure tone & speech audiometry results
Increased hearing threshold at different frequencies was observed in 60.87% (56/92) of ears examined (versus 20% [16/80] for control subjects), ($p < 0.01$). Of them, bilateral and unilateral SNHL and bilateral MHL were reported in 32.61% (15/46), 10.87% (5/46) and 17.39% (8/46) of the patients, respectively. Mild and moderate SNHL were reported in 35.71% (20/56) and 64.29% (36/56), respectively. Table 2 showed PTA thresholds of the studied groups. Table 3 shows the results of Speech Reception Threshold (SRT) and Speech Discrimination Score (SDS). It shows that patients had significant poor SRT and SDS compared with controls. The results of speech audiometry were consistent with that of PTA as evident from the significant higher values ($p < 0.001$) of SRT with a mild reduction of SDS ($p < 0.015$). Approximately 17.39% (8/46) had type (B) tympanograms indicating middle ear problem. The stapedius reflex levels were consistent with pure tone thresholds of these subjects.

TEOAEs results
Table 4 showed results of TEOAEs echo level (amplitude changes in dB SPL). TEOAE results of 3.0–4.0 kHz amplitude values were significantly lower in the study group compared with controls. Thirty-six ears of the patients (39.13% or 36/92) and 12 ears (15%) of the controls demonstrated significant reduction in TEOAEs response level.

ABR results
Table 5 showed the results of ABR in the studied groups at 90 dBHL with low and high repetition rate frequencies. ABR results showed significant prolongation of absolute latencies of waves I, III and V and IPLs particularly at high repetition rate frequencies when compared with the control group. Prolonged wave I latency was observed in 42 (45.65%) ears examined. Prolonged III–V and I–V IPLs were observed in 36 (39.13%) and 16 (17.39%) ears examined, respectively. Twenty-two (78.57%) patients had combination of more than one abnormality in different audiometric testing.

ate correlations were examined between dependent variables and the independent variables or confounders (e.g., age and duration of illness) (r and p values). The model was adjusted for age as a confounder in the mul-

Table 2. Pure tone audiometry thresholds of the studied groups.				
Frequency (Hz)	Patients		Controls	
	Right	Left	Right	Left
250	13.92 ±5.79	12.81 ±4.62	12.51 ±3.80	13.03 ±1.50
500	15.93 ±6.42[†]	17.46 ±7.52[†]	6.62 ±1.56	7.06 ±3.10
1000	17.55 ±9.79[†]	16.69 ±5.80[†]	9.05 ±2.67	8.99 ±2.87
2000	16.58 ±7.37[†]	18.08 ±9.26[†]	8.19 ±3.25	7.19 ±1.15
4000	22.56 ±12.44[†]	23.55 ±7.84[†]	12.81 ±6.57	11.91 ±2.57
8000	24.97 ±15.33[†]	24.83 ±8.06[†]	11.00 ±2.27	10.00 ±1.47

[†]p< 0.01.
Data are expressed as mean ±SD.

We reported no significant differences in the demographic, clinical, laboratory and audiologic results between seropositive and seronegative RA patients (Table 6).

Correlations between demographic, clinical and laboratory variables and audiologic variables showed: (1) significant associations were identified between patients 'age and (a) hearing thresholds at 250 Hz (r = 0.418, p = 0.004), 500 Hz (r = 0.484, p = 0.001), 1000 Hz (r = 0.418, p = 0.004), 2000 Hz (r = 0.477, p = 0.001), 4000 Hz (r = 0.479, p = 0.001), 8000 Hz (r = 0.587, p = 0.0001), (b) wave I (r = 0.366, p = 0.024) and wave III (r = 0.386, p = 0.014) absolute latencies and I–V IPL (r = 0.528, p = 0.001) of ABR at high repetition rate frequencies and (c) TEOAEs amplitudes at 4 kHz (r = -0.599; p < 0.05); (2) significant associations between duration of illness and (a) hearing thresholds at 2000 Hz (r = 0.547, p = 0.0001), 4000 Hz (r = 0.626, p = 0.0001), 8000 Hz (r = 0.680, p = 0.0001), (b) III–V (r = 0.479, p = 0.005) and I–V (r = 0.557, p = 0.001) IPLs of ABR at high repetition rate frequencies and (c) TEOAEs levels at 4 kHz (r = -0.638, p < 0.001) and 3); no significant associations between RF and audiometric variables. In multivariate analysis and after adjustment of age, the duration of illness was significant for values of I–V IPL (OR: 2.90, 95% CI: 1.20–6.80, p = 0.032) and TEOAEs at 4 KHz(OR: 3.86, 95% CI: 1.23–6.80, p = 0.004).

Although it is not our aim, 17 patients (36.96%) had mononeuritis multiplex and 25 (54.35%) had bilateral sensory neuropathy in both lower limbs (sural nerves) suggesting peripheral nervous system involvement.

Discussion

Hearing impairment is a frequent extra-articular manifestation of RA. In this study, nearly two-thirds of the studied patients had abnormalities in one or more audiometric testing indicative of SNHL. In PTA, we reported higher hearing thresholds at different frequencies in nearly 61% (28/46) of the examined ears. The results of speech audiometry were in accordance to that of PTA. Varying frequencies of SNHL were previously reported with RA and ranged from 24 to 60% [6,8,13]. SNHL was observed as higher hearing thresholds at different frequencies (500–8000 Hz) [6,8]. In addition to increased hearing thresholds, others reported abnormalities of tone decay test, speech reception threshold, speech discrimination score and short increment sensitivity index tests [15].

In this study, we reported bilateral MHL in 17.35% of patients examined in the form of increased hearing thresholds at low and middle frequencies, higher air–bone gaps in PTA and abnormal tympanometry. Several studies reported varying frequencies of pure CHL or MHL with RA at different frequencies. Pure CHL was reported in 1.9–70.5% [6,8,12], while MHL was reported in 10.8–24% [15,16] of RA patients studied. Halligan et al. [16] in their study on 29 patients with RA, reported hearing impairment in 59% in which SNHL was reported in 45%, with 14% of mixed or

Table 3. Speech reception threshold and speech discrimination score for all ears.			
	Patients range mean ±SD	Control range mean ±SD	p-value
Speech reception threshold	5–35	5–10	0.001[‡]
	15.20 ±5.65	6.56 ±2.39	
Speech discrimination score	92–100	100–100	0.015[†]
	94.53 ±2.42	100 ±0.00	

[†]p < 0.05.
[‡]p < 0.001.

Frequency (kHz)	Patients		Controls		p-value
	Right	Left	Right	Left	
Overall echo level (range)	0.00–20.00	0.00–22.00	1.40–19.80	0.00–20.00	P1a = 0.541
Mean	12.56	12.25	10.46	12.20	P1b = 0.098
25th percentile	9.30	10.60	7.80	9.20	
50th percentile	13.30	12.60	10.46	13.40	
75th percentile	16.38	14.63	13.35	14.90	
1.0 (range)	-3.00–22.00	-3.00–18.00	-5.00–25.00	-1.00–24.00	P1a = 0.076
Mean	8.20	9.46	10.95	10.73	P1b = 0.542
25th percentile	6.75	5.20	8.00	6.00	
50th percentile	9.82	9.00	10.00	11.00	
75th percentile	12.25	11.00	14.50	14.50	
1.5 (range)	-2.00–24.00	-3.00–25.00	2.00–24.00	1.00–25.00	P1a = 0.304
Mean	11.20	13.54	12.25	11.80	P1b = 0.827
25th percentile	8.00	9.65	10.00	7.00	
50th percentile	11.00	11.65	13.00	12.00	
75th percentile	16.75	17.08	17.00	18.00	
2.0 (range)	-5.00–25.00	-2.00–26.00	0.00–27.00	0.00–24.00	P1a = 0.206
Mean	11.54	11.62	13.22	11.84	P1b = 0.864
25th percentile	9.00	7.75	11.00	6.50	
50th percentile	12.00	12.00	13.00	13.00	
75th percentile	16.00	15.25	16.00	16.00	
3.0 (range)	0.00–24.00	-3.00–21.00	-2.00–24.00	-1.00–20.00	P1a = 0.025
Mean	7.32	6.45	12.59	10.27	P1b = 0.050
25th percentile	4.50	2.65	8.50	4.00	
50th percentile	8.00	10.00	13.00	12.00	
75th percentile	15.00	15.25	16.50	13.50	
4.0 (range)	-4.00–23.00	-4.00–21.00	0.00–24.00	-3.00–18.00	P1a = 0.019
Mean	7.45	6.46	10.73	7.59	P1b = 0.410
25th percentile	5.20	1.75	8.00	3.00	
50th percentile	8.00	7.50	11.00	8.00	
75th percentile	12.00	12.25	14.50	13.00	

Significance: P1a, b: right and left for patients versus controls.

pure CHL. In addition to increased hearing thresholds and higher air bone gap, others reported immitance abnormalities, ossicular joints immobility on high resolution computed tomography (HRCT) as sclerosed oval window and shift of the resonance towards higher frequencies on multiple frequency tympanometry (MFT) [9,33].

In this study, we reported abnormal TEOAEs in 39.13% of the ears examined in the form of reduced amplitude of TEOAEs values at 3.0–4.0 kHz indica-tive of cochlear pathology. In general, otoacoustic emissions (OAEs) permit sensitive assessments of cochlear function before functional and significant hearing loss occur from any cause. It is more sensitive than PTA in detection of cochlear pathology [34]. TEOAE is known to originate from the activation of the whole cochlea [35–38]. It indicates impairment of electromotility of OHCs in response to the electrical stimulations. Decreased reproducibility and amplitude of TEOAEs values were previously reported in patients with RA [13].

In this study, we reported prolonged wave I latency in 45.65% (42/92) ears examined indicative of auditory nerve pathology. While 56.52% (52/92) of ears examined had prolonged III–V and I–V IPLs indicative of prolonged brainstem conduction time, that is, brainstem pathway pathology. An increase in wave I latency and prolonged III–V and I–V IPLs [12] of ABR were previously reported with RA. It has been suggested that abnormal audiometric results and normal ABR are compatible with cochlea involvement while abnormal audiometric results associated with an altered ABR and stapedial reflex test are compatible with retrocochlear involvement [12]. It is known that wave I is derived from the auditory nerve, wave III is derived from the auditory nuclei in mid and rostral regions of the brainstem and wave V probably comes from the lateral lemniscus and I–V interpeak latency is regarded as brainstem conduction time [39].

In this study, although 65.22% (30/46) of the patients were seropositive (as indicated by elevated RF), we did not identify differences in values of audiometric testing between them and seronegative patients or significant correlations between RF and audiometric values. In accordance, Elwany et al. [6] found no relationship between RA activity and hearing loss. Kakani et al. [15] reported no statistical corre-

lation between hearing loss or otoadmittance abnormality (indicative of CHL) and duration or activity of RA or positivity of RF. Murdin et al. [12] observed no relationship between hearing thresholds and markers of disease activity or other rheumatological parameters. In contrast, Poorey et al. [40] reported a direct relationship between the prevalence of abnormal otoadmittance and positivity of RA factor and staging and activity of the disease. Bakr et al. [9] identified significant correlation between disease activity and extra-articular findings with impaired amplitude value and reproducibility of TEOAEs. Takatsu et al. [10] reported that the presence of SNHL was related to ESR ($p < 0.05$), plasma interleukin-6 ($p < 0.05$) and plasma matrix metalloproteinase-3 ($p < 0.001$). Dikici et al. [13] observed an association between the active stage of the disease and the diminished hearing thresholds and between the higher Brinkman Index values and the decreased TEOAE values. The authors also observed decrease in compliance values in patients with higher Ritchie Articular Index, CRP, ESR and platelet counts and longer disease duration. Despite these controversies, we believe that seronegativity does not exclude the presence of extra-articular manifestations [41]. The heterogeneity and the chronicity of the disease process may contrib-

ABR	Patients		Controls	
	Right	**Left**	**Right**	**Left**
ABR at 90 dBHL low repetition: wave latencies				
I	2.98 ±0.86[†]	2.75 ±0.68[†]	1.68 ±0.18	1.75 ±0.11
III	4.92 ±0.59	4.89 ±0.66	3.22 ±0.14	3.55 ±0.13
V	6.86 ±0.80[†]	6.91 ±0.86	5.00 ±0.42	5.55 ±0.24
Interpeak latencies				
I–III	3.81 ±1.23[†]	3.92 ±1.53	2.04 ±0.25	2.03 ±0.18
III–V	3.89 ±0.75[†]	3.72 ±0.33	1.87 ±0.35	2.00 ±0.16
I–V	5.50 ±0.77[†]	4.89 ±0.74	3.07 ±0.60	4.13 ±0.13
ABR at 90 dBHL high repetition: wave latencies				
I	2.51 ±0.28[†]	3.40 ±0.52[†]	1.74 ±0.18	1.80 ±0.15
III	4.96 ±0.32[†]	4.91 ±0.20	3.54 ±0.62	3.64 ±0.74
V	5.88 ±0.31	6.91 ±0.27	5.39 ±0.74	5.06 ±0.61
Interpeak latencies				
I–III	3.64 ±1.06‡	2.83 ±1.12	1.98 ±0.21	2.08 ±0.21
III–V	3.93 ±0.21‡	4.10 ±0.15‡	1.74 ±0.23	1.89 ±0.23
I–V	5.81 ±0.63[†]	5.67 ±0.23‡	3.69 ±0.39	3.69 ±0.62

Table 5. The results of auditory-brainstem response in the studied groups at 90 decibel hearing level with low and high repetition rate frequencies.

[†]$p < 0.05$.
‡$p < 0.01$.
Data are expressed as mean ± SD.

ute in the change of seropositivity to a great extent. In addition, the modulation of the serology due to the antirheumatic drug effect cannot be excluded as a cause of seronegativity. Recent studies suggested that inflammatory marker levels from a single time point were not associated with an increased risk of develop-

Table 6. Comparisons between demographic, clinical, audiologic results of patients with rheumatoid arthritis patients according to serology.		
	Seropositive (n = 30)	Seronegative (n = 16)
Demographic & clinical results		
Age at presentation (years)	47.37 ±11.99	43.50 ±10.79
Duration of illness (years)	9.22 ±5.83	10.28 ±5.14
Morning stiffness (min)	90.63 ±44.12	87.22 ±55.58
Number of active joints	7.31 ±4.94	5.25 ±2.97
Richie articular index (RAI)	13.94 ±8.71	10.75 ±8.96
Pain scale (VAS)	6.00 ±1.82	5.13 ±2.10
Functional capacity (range: 1–4)	1.53 ±0.61	1.47 ±0.0.81
X-ray grading (G0–4)		
G1	7 (15.22%)	3 (6.52%)
G2	17 (36.96%)	9 (19.56%)
G3	6 (13.04%)	2 (4.35%)
G4	0	2 (4.35%)
Subcutaneous nodules (SN)	2 (6.67%)	6 (13.04%)
PTA		
PTA threshold (Hz)		
250	13.06 ±7.52	16.74 ±5.24
500	18.09 ±6.85	16.23 ±5.32
1000	17.39 ±5.30	14.55 ±8.45
2000	18.89 ±6.66	16.67 ±7.66
4000	25.85 ±6.55	22.85 ±9.55
8000	29.33 ±10.25	25.07 ±13.66
TEOAEs		
Overall echo level (kHz; range [mean])	0.00–20.00 (12.56)	0.00–22.00 (12.25)
1.0	-3.00–22.00 (8.20)	-3.00–18.00 (9.46)
1.5	-2.00–24.00 (11.20)	-3.00–25.00 (13.54)
2.0	-5.00–25.00 (11.54)	-2.00–26.00 (11.62)
3.0	0.00–24.00 (7.32)	-3.00–21.00 (6.45)
4.0	-4.00–23.00 (7.45)	-4.00–21.00 (6.46)
ABR at 90 dBHL low repetition: wave latencies		
I	2.99 ±0.56	2.55 ±0.68
III	4.88 ±0.45	4.44 ±0.23
V	6.88 ±0.80	5.75 ±0.45
Interpeak latencies		
I–III	3.56 ±0.20	3.92 ±1.53
III–V	3.76 ±0.55	3.55 ±0.22
I–V	5.89 ±0.90	4.43 ±0.56
ABR: Auditory-brainstem response; PTA: Pure tone audiometry; TEOAEs: Transient evoked otoacoustic emissions.		

Table 6. Comparisons between demographic, clinical, audiologic results of patients with rheumatoid arthritis patients according to serology (cont.).		
	Seropositive (n = 30)	Seronegative (n = 16)
ABR at 90 dBHL high repetition: wave latencies		
I	2.66 ±0.25	2.22 ±0.12
III	4.88 ±0.15	4.91 ±0.20
V	6.88 ±0.30	5.90 ±0.05
Interpeak latencies		
I–III	3.67 ±0.26	2.66 ±0.52
III–V	4.20 ±0.57	3.10 ±0.35
I–V	5.68 ±0.43	6.07 ±0.03
ABR: Auditory-brainstem response; PTA: Pure tone audiometry; TEOAEs: Transient evoked otoacoustic emissions.		

ing hearing impairment. However, subsequent observation of the patients may provide significant association between long-term serum C-reactive protein levels and hearing impairment [42].

In this study, we reported significant associations between duration of illness and hearing thresholds at higher repetition rate frequencies (2000–8000 Hz), III–V and I–V IPLs of ABR and TEOAEs levels at 4 kHz [9,43]. Bakr *et al.* [9] reported that the changes in TEOAEs were significantly correlated with the duration of RA. Salvinelli *et al.* [43] reported significant correlation between disease duration and echo amplitude in TEOAEs. Dikici *et al.* [13] observed an association between disease duration, RA nodules and higher methotrexate cumulative doses and the increase in hearing thresholds and the decrease in TEOAE values.

We suggest that SNHL may be due to the following: First: The chronic inflammatory course of the disease (i.e., recurrent active stages of the disease followed by fibrosis) and its accompanied destructions of hearing organ at multiple locations may lead to auditory neuropathy, cochlear damage and damage of the auditory pathway within the brainstem (e.g., middle and inner ear and auditor pathways). We suggest that cochlear pathology or auditory neuropathy due to vasculitis or arteritis of the *vasa nervosum* with reduction of blood flow or disturbances of its vasculature due to antigen-antibody complex immunologically damaging process with inflammatory reaction associated with RA as causes of hearing impairment [11,14,44]. It is well known that the cochlea is a vascular region provided with terminal capillary bed. The high metabolic demands of the inner ear and the inherited properties of the cochlea making it unable to form collateral vessels that could restore blood flow in destructed regions. In support, hearing impairment is present in patients with mononeuritis multiplex and bilateral sensory neuropathy suggesting vasculitis [45–47]. Second, one can speculate that RA may aggravate age-related hearing loss [48,49]. In this study, we reported significant associations between patients 'age and hearing thresholds at different frequencies, wave I and wave III of ABR at high repetition rate frequencies and TEOAEs levels at 4 kHz. In accordance, Bakr *et al.* [9] reported that the changes in TEOAEs were significantly correlated with the age of the subjects as there was decrease in the amplitude and whole reproducibility with advancement of the age and prolongation of the disease duration. Pascual-Ramos *et al.* [50] reported that patients with RA and having hearing loss were significantly older (p ≤ 0.001), had more frequent rheumatoid nodules (p = 0.001), and had more comorbidities. They also reported that in multivariate analysis hearing loss was significantly associated with age (odds ratio, 1.1; 95% confidence interval, 1.03–1.15; p ≤ 0.001). The best cutoff level for hearing loss was found to be 50 years of age and increased to 59 years for moderate/severe hearing loss. Third, although we did not find a significant association between anti-rheumatic drugs (as chloroquine, NSAIDS and methotrexate) and the abnormal neurophysiological findings, however, the possibility of ototoxicity from anti-rheumatic drugs cannot be excluded [6,13,18].

Despite the importance of the results of this study, there are some limitations which include: relatively small number of patients; we used RF as the only immune marker of seropositivity which seems by many studies impractical and more than one antibody marker should be utilized to assure the diagnosis; and due to the cross-sectional design of this study, the temporal relation between the appearance of auditory dysfunction in patients with RA is unknown.

Conclusion
Hearing loss is a common complication of RA. Both peripheral and central hearing impairments can occur as

a result of the disease process. Future-related researches are also important and have to include the following: longitudinal studies that prospectively assess the relation of the disease process over time on auditory functioning of patients with RA; and randomized clinical trials that prospectively compare auditory function in response to different treatment modalities including immunotherapy, vasodilator, antioxidants versus a control group of RA patients.

Future perspective

The knowledge that the auditory pathways (central and peripheral) are involved in RA is important for specialists serving those patients and thus frequent evaluation by audiometric tests in RA patients is recommended for controlling hearing disorders by therapeutic and rehabilitation procedures.

Executive summary

Background
- Patients with rheumatoid arthritis (RA) may develop extra-articular manifestations, among is auditory dysfunction. We aimed to determine the peripheral and central auditory pathways functions with RA.

Patients & methods
- Included were 46 adult females (<50 years old) with RA and 40 matched healthy subjects. Peripheral and central hearing functions were assessed using a comprehensive set of audiometric tests which include pure air and bone tone audiometry (PTA), transient evoked otoacoustic emissions (TEOAEs) and brainstem-auditory response (ABR).

Results
- Compared to controls, increased hearing thresholds at different frequencies were observed in 60.87% (56/92) of ears examined. Sensorineural (SNHL) and mixed (conductive and SNHL) hearing losses of mild and moderate severities were reported.
- TEOAE results of 3.0–4.0 kHz amplitude values were significantly lower in 39.13% of the examined ears.
- ABR results showed significant prolongation of absolute latencies of waves I, III and V and IPLs particularly at high repetition rate frequencies when compared with the control group. Prolonged wave I latency and III–V and I–V IPLs were observed in 42 (45.65%), 36 (39.13%) and 16 (17.39%) of the ears examined, respectively.
- Significant associations were identified between the duration of illness and values of I–V IPL and TEOAEs at 4 KHz even after adjustment with patients' age.
- No significant associations were identified between RF and audiometric variables.

Conclusion
- This study indicates that: 1) hearing loss is a frequent complication of RA, 2) conductive, sensorineural and mixed hearing impairments are common with RA, 3) Pathologies of the auditory nerve, cochlea and auditory pathway within the brainstem are causes of SNHL with increased chronicity of RA, 4) Peripheral and/or central auditory pathways dysfunction with RA could be a result of inflammatory disease process, vasculitis or an adverse effect of anti-rheumatic medications, 5) TEOAEs recordings are more sensitive for detection of cochlear damage with RA compared with basic audiological testing, and 6) accordingly, auditory issues are important to be considered in the therapeutic and preventive strategies for patients with RA.

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