

# Assessment of the audiovestibular system in patients with rheumatoid arthritis

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## Objective

This study was designed to assess hearing and vestibular function in patients with rheumatoid arthritis (RA) in comparison with a control group. In addition, we correlated these findings in disease activity and severity.

## Materials and methods

Totally, 40 RA patients (35 women and five men) diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria and 20 healthy controls (11 women and nine men), whose age ranged from 25 to 66 years with a mean age of 45.5±12.4 years, were included in the study. Each individuals was tested with pure tone audiometry. Mean values of air and bone conduction at each frequency and tympanometric values were calculated for the study groups. Videonystagmography (VNG) test including smooth pursuit, saccade, optokinetic tests, positioning tests, positional test, and water caloric tests was also carried out.

## Results

The mean air conduction threshold values at high frequencies (4000 and 8000 Hz) in the RA group were lower than in the control group. The difference between mean air conduction threshold values of the control group and the RA group at high frequencies was statistically significant ( $P<0.05$ ). There was no statistically significance between the two groups as regards speech reception threshold, speech discrimination (DIS), and tympanometric values ( $P>0.05$ ). VNG testing revealed central abnormalities in 12 (30%) patients, peripheral abnormalities in nine (22.5%) patients, and mixed abnormalities in one (2.5%) patient. There was no association between VNG abnormalities in patients with RA and age, sex, duration of disease, accompanying vertigo complaint, and the laboratory findings ( $P>0.05$ ).

## Conclusion

There is an association between RA and audiovestibular system dysfunction regardless clinical and demographic situation of patients. We assume that the shearing and vestibular disturbances in RA are more prevalent than previously recognized. High-frequency hearing loss in RA patients could be an indicator of cochlear involvement.

## Keywords:

hearing loss, high frequency, rheumatoid arthritis, videonystagmography findings

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## Introduction

Rheumatoid arthritis (RA), a multifactorial autoimmune disease affecting 1% of the population, is characterized by the recruitment of leukocytes, primarily CD4<sup>+</sup> T-cells, and monocytes from the vasculature into inflamed synovial tissue and synovial fluid, eventually leading to a chronic inflammation [1]. The prevalence of RA increases with age, and more women than men are affected. Extra-articular manifestations of the disease involve multiple organ systems. Cardiac, pulmonary, skin, and eye involvements are some examples. The temporomandibular joint, cervical spine, larynx, and inner ear can be involved in the head and neck [2].

RA could affect hearing through a number of different putative mechanisms. First, as an inflammatory

arthritis, the synovial incudostapedial and incudomalleolar joints could be directly involved, causing a conductive hearing loss. Second, there is possibility that a vasculitis could cause a true auditory neuropathy, perhaps as part of a mononeuritis multiplex. Third, the autoimmune process could cause inflammatory destruction of the cochlear hair cells or the inner ear could be the site of immune complex deposition. Fourth, some of the drugs, which are used to treat RA, are known to affect the ear. These include salicylates and other

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nonsteroidal anti-inflammatories, antimalarial, and some other disease-modifying agents [3–5].

With respect to the auditory system, conflicting findings were found, both as to the type of hearing loss that may occur and as to whether markers of RA disease activity and severity correlate with hearing levels [6–8].

Ferrara *et al.* [1] reported evidence of vestibular dysfunction in several patients diagnosed with RA. However, Kakani *et al.* [2] failed to demonstrate abnormal caloric responses or abnormal saccadic eye movements in patients with RA, although some patients reported occasional dizziness in their daily lives. Wennmo and Wennmo [9] reported that one possibility is that some RA patients experience dizziness as a side effect of some of the medications that they use, for example, nonsteroidal anti-inflammatory drugs. Yilmaz *et al.* [10] suggested an association of RA and vestibular system dysfunction regardless of age, sex, and duration of disease, presence of vertigo complaint, the results of laboratory testing, sensorineural hearing loss (SNHL), or medications.

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## Aim

The aim of the present study was to assess hearing and vestibular function in patients with RA in comparison with a control group. In addition, we correlated these findings with disease activity and severity.

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## Materials and methods

This case–controlled study was conducted on 40 RA patients (35 women and five men) diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria and 20 healthy controls (11 women and nine men), whose age ranged from 25 to 66 years with a mean age of  $45.5 \pm 12.4$  years. The study was approved by the ethical committee of the department and consents were obtained from all participants. Cases were collected from Beni-Suef University Hospital. The study took place during the period from February 2015 to May 2016.

Disease activity had been evaluated according to the following criteria: erythrocyte sedimentation rate (ESR) at least 50 mm/h, rheumatoid factor (RF) positivity, six or more tender joints, three or more swollen joints, and morning stiffness of at least 30 min duration. All patients had been using nonsteroidal anti-inflammatory drugs, systemic steroids, and methotrexate.

## Exclusion criteria

Individuals who had any otological or neurological disorder, history of ototoxic drugs usage, or noise exposure were excluded from the study.

All individuals who participated in this study were subjected to the following:

- (1) Full history taking.
- (2) Otological examination.
- (3) Audiological evaluation: tonal audiometry in the frequency range of 250–8000 Hz, using Madsen Orbiter 922 (Otometrics, Denmark) in a sound-treated room with a TDH 39 earphones (Grason-Stadler, USA); speech audiometry including speech reception threshold (SRT) using Arabic spondee words [11]; and word discrimination score (WDS) using Arabic phonetically balanced words [12].
- (4) Immittanceometry: this was carried out using GSI 33 (Grason-Stadler, USA) using single-component, single-frequency tympanometry with a probe tone of 226 Hz. Testing of the acoustic reflex threshold, for ipsilateral and contralateral elicited reflexes, was carried out using pure tones at 500, 1000, 2000, and 4000 Hz.
- (5) Vestibular system evaluation: this was carried out using videonystagmography (VNG) ICS Chart 200 that included the following:
  - (a) Smooth pursuit testing: the patients were asked to visually follow a target on the light bar that moved in the horizontal plane at the 0.2–0.7 Hz. The computer then calculated the gain of smooth pursuit. A gain of less than 70% indicated impairment.
  - (b) Saccade testing: the patients were asked to fixate on a visual target on the light bar. The target jumped to the right and left with amplitudes ranging from 5° to 25°. The computer then calculated the values for latency, accuracy, and peak velocity. Latency of more than 280° ms, accuracy of less than 80%, and peak velocity of less than 300° were considered abnormal. The patient with prolonged latency was diagnosed as having impaired saccadic movement if at least one of the accuracy or peak velocity scores was also outside the reference range.
  - (c) Positional tests: the eye movements of each patient were recorded for 30 s without visual fixation. The patient had been placed in the sitting, supine, right ear down, left ear down position, right side, left side, and head-hanging positions. (d) Positioning test (Dix–Hallpike test): each patient was seated with his or her head positioned 45° to the right

or left before being pulled quickly to the head-hanging position over the end of the examining table. The examiner observed each patient's eye movements for at least 30 s. Then the patient was returned to the sitting position.

- (d) Water caloric tests: bithermal caloric tests were performed; each ear was irrigated with water at temperatures of 30 and 44°C for 40 s. The recordings of responses were conducted for 3 min. Canal paresis and directional preponderance were calculated according to Jongkees' formula [13]. Values greater than 20% for canal paresis and 25% for directional preponderance were considered abnormal.

### Statistical methods

Data were coded and entered using the statistical package statistical package for the social sciences, version 23 (SPSS; SPSS Inc., Chicago, Illinois, USA). Quantitative data were summarized using mean, SD, median, minimum, and maximum, and categorical data using frequency (count) and relative frequency (percentage). For comparison of serial measurements within each patient, the nonparametric Friedman test and Wilcoxon signed rank test were used [14]. The Mann-Whitney test was used to compare two unrelated samples. The Pearson correlation coefficient was used to evaluate the relationship between two quantitative variables.

*P*-values less than 0.05 were considered statistically significant.

### Results

The current case-controlled study was carried out on 40 RA patients (35 women and five men) diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria and 20 healthy controls (11 women and nine men), with age ranging from 25 to 66 years with a mean age of 45.5±12.4 years. There was no statistical significance between the two groups as regards sex ( $P>0.05$ ).

Table 1 showed the mean right ear hearing thresholds in patients with RA and that of the control group. At frequencies 250, 500, 1000, and 2000 Hz, the difference between both groups was not statistically significant ( $P>0.05$ ). Whereas the mean of hearing thresholds in patients with RA was lower than that of the control group at high frequencies (4000, 8000 Hz) and this difference was statistically significant ( $P<0.05$ ).

Table 2 showed the mean left ear hearing thresholds in patients with RA and that of the control group. At frequencies 250, 500, 1000, and 2000 Hz, the difference between both groups was not statistically significant ( $P>0.05$ ). Whereas the mean of hearing thresholds in patients with RA was lower than that of the control group at high frequencies (4000, 8000 Hz) and this difference was statistically significant ( $P<0.05$ ).

Table 3 showed comparison of VNG results as regards pursuit test, saccade test, optokinetic test, positional test, Dix-Hallpike test, and water caloric test, and as regards vertigo complaint between the RA and the control groups, the difference was not statistically significant ( $P>0.05$ ), except for the saccade test and

**Table 1 Mean±SD of hearing threshold levels of rheumatoid arthritis patients and the control group in the right ear**

	Patients (n=40) (mean±SD)	Controls (n=20) (mean±SD)	<i>P</i> value	Significance
PTA 250 Hz	20.4±5.7	19.8±4.4	0.670	NS
PTA 500 Hz	21.3±5.6	19.8±4.1	0.295	NS
PTA 1000 Hz	21.5±6.2	20.5±3.6	0.509	NS
PTA 2000 Hz	25±10.1	21.8±2.9	0.164	NS
PTA 4000 Hz	33.5±15.4	23.8±2.2	0.007	HS
PTA 8000 Hz	33±14.1	23.5±2.4	0.004	HS

HS, highly significant; PTA, pure tone audiometry.

**Table 2 Mean±SD of hearing threshold levels of rheumatoid arthritis patients and the control group in the left ear**

	Patients (n=40) (mean±SD)	Controls (n=20) (mean±SD)	<i>P</i> value	Significance
PTA 250 Hz	19.1±5.0	20±3.6	0.493	NS
PTA 500 Hz	20.5±4.9	21.3±3.9	0.555	NS
PTA 1000 Hz	21.9±5.5	21.3±3.2	0.641	NS
PTA 2000 Hz	23.4±8.4	20.3±4.4	0.124	NS
PTA 4000 Hz	31.8±15.7	23.3±2.4	0.020	S
PTA 8000 Hz	33.9±15.7	24.8±7.5	0.017	S

S, significant.

water caloric the difference was statistically significant ( $P < 0.05$ ). As regards vertigo complaint, there was a statistically significant difference between the two groups.

Table 4 showed that there was a correlation between impaired pursuit test in patients with RA and duration of RA and RF. This correlation was statistically significant ( $P < 0.05$ ). In addition, there was a correlation between impaired water caloric test in patients with RA and RF and this correlation was statistically significant ( $P < 0.05$ ). As regards impaired saccade test in patients with RA, there was not any correlation between the test and age, sex,

duration of RA, laboratory findings, and vertigo complaint.

## Discussion

RA is a chronic multisystemic autoimmune disorder characterized by inflammation of the synovial membranes of the diarthrodial joints, which may be followed by cartilage destruction, bone erosion, and weakening and destruction of the ligaments, tendons, and joint capsules [15]. The cervical vertebrae, temporomandibular joint, larynx, and audiovestibular system can be the sites of involvement in the head and neck [13].

**Table 3 Comparison between rheumatoid arthritis patients and the control group as regards videonystagmography results and vertigo complaint**

VNG	Patients (n=40) [n (%)]	Controls (n=20) [n (%)]	P value	Significance
Pursuit test				
Normal	35 (87.5)	20 (100)	0.120	NS
Abnormal	5 (12.55)	0 (0)		
Saccade test				
Normal	29 (72.5)	20 (100)	0.007	HS
Abnormal	11 (27.5)	0 (0)		
Optokinetic test				
Normal	40 (100)	20 (100)	1	NS
Abnormal	0 (0)	0 (0)		
Positional test				
Normal	40 (100)	20 (100)	1	NS
Abnormal	0 (0)	0 (0)		
Dix–Hallpike test				
Normal	40 (100)	20 (100)	1	NS
Abnormal	0 (0)	0 (0)		
Water caloric test				
Normal	31 (77.5)	20 (100)	0.022	S
CP	9 (22.5)	0 (0)		
Vertigo complaint				
No	12 (30)	20 (100)	0.001	HS
Yes	28 (70)	0 (0)		

CP, canal paresis; HS, highly significant; VNG, videonystagmography.

**Table 4 Correlation between videonystagmography results and age, sex, duration of disease, vertigo complaint, laboratory findings, and vertigo complaint in rheumatoid arthritis patients**

	Pursuit test		P value	Saccade test		P value	Water caloric test		P value
	Abnormal	Normal		Abnormal	Normal		Abnormal	Normal	
Individuals [n (%)]	5 (13.5)	35 (87.5)		11 (27.5)	29 (72.5)		9 (22.5)	31 (77.5)	
Age (years)	51±13.2	41.9±12.2	0.130	46.2±13.1	41.8±12.3	0.327	49.5±10	41.1±12.6	0.074
Sex (female/male)	3/2	28/7	0.311	9/2	22/7	0.523	24/7	7/2	0.680
Duration of RA	10.2±3	4.5±2	0.001**	6.4±2.6	4.8±2.8	0.108	5.2±1.7	5.2±3.1	0.998
Laboratory findings [n (%)]									
RF	3 (60)	0 (0)	0.001**	2 (18.2)	1 (3.4)	0.178	3 (33.3)	0 (0)	0.008**
Anti-CCP	5 (100)	34 (97.1)	0.998	10 (90.9)	29 (100)	0.275	9 (100)	30 (96.8)	0.999
CRP	2 (40)	2 (5.7)	0.068	1 (9.1)	3 (10.3)	0.998	0 (0)	4 (12.9)	0.557
ESR	3 (60)	7 (20)	0.089	4 (36.4)	6 (20.7)	0.417	1 (11.1)	9 (29)	0.404
Vertigo complaint [n (%)]	5 (100)	23 (65.7)	0.298	8 (72.7)	20 (69)	0.988	8 (88.9)	20 (64.5)	0.233

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor.

SNHL has been widely investigated in people with RA, in whom the SNHL rate varies from 24 to 60% [3]. Despite the cause of hearing loss in RA is not fully understood, the arthritic joint involvements in the middle ear ossicular chain, inflammation of the eighth cranial nerve, vasculitis of labyrinthine vessels, and ototoxic effects of medications used for the treatment have been generally accounted for this condition [2,15].

In the present study, we found that the difference between mean hearing thresholds of both right and left ears in patients with RA and in the control group at frequencies 250, 500, 1000, and 2000 Hz was not statistically significant ( $P>0.05$ ). Whereas at high frequencies (4000, 8000 Hz) the mean of hearing thresholds in patients with RA was lower than that of the control group and this difference was statistically significant ( $P<0.05$ ) (Tables 1 and 2). We also found that SNHL was greater than 25 dB in 15 (37.5%) of RA patients. In almost all cases, hearing loss was bilateral and symmetrical.

Our results were in agreement with Gussen [16] who reported that a slight bilateral high-frequency hearing loss was seen in patients with RA. But, Murdin *et al.* [17] found that hearing loss was predominantly at low frequencies and middle frequencies. A more likely hypothesis is that this is an earlier disease manifestation, which was confirmed by the young age of the individuals. Endolymphatic hydrops is one pathological process known to be associated with RA that presents with low-frequency hearing losses and later progresses to the high frequencies, although the study individuals did not report the typical vertiginous attacks expected with this presentation [18].

Goodwill *et al.* [19] found no relationship between the activity of RA and the incidence of SNHL, but they reported a greater incidence of SNHL in patients with rheumatoid nodules. Moreover, Takatsu *et al.* [20] reported that they could find no association between hearing loss, RA, and autoimmunity, but inner ear involvement correlated with ESR, plasma interleukin-6, and metalloproteinase-3. They suggested that these mediators of systemic inflammation could cause inner ear dysfunction through tissue damage.

Halligan *et al.* [21] found that there was no difference found in objective audiometric measurements in patients with RA compared with controls. Subjectively, patients with RA were more likely to perceive themselves as having hearing disturbances,

which may be related to overall disease not related to functional impairment.

In the present study, VNG test results revealed that smooth pursuit was impaired in five (12.55%) patients with RA, but in the control group there was no individuals with impaired smooth pursuit. The difference between the two groups was not statistically significant ( $P>0.05$ ). Optokinetic, Dix-Hallpike tests, or positional tests were carried out but they did not reveal any abnormalities in the RA group or in the control group. Despite 11 (27.5%) patients with RA exhibiting impaired Saccade testing, this parameter was found to be within normal limits in all controls. The difference between the two groups regarding saccadic testing was statistically significant ( $P<0.05$ ). Saccade tracing abnormalities were undershoots in eleven patients with RA but two of them also showed a prolonged latency. Canal paresis was identified in nine (22.5%) patients with RA, but no individuals in the control group demonstrated this findings. The difference between the two groups regarding canal paresis was statistically significant ( $P<0.05$ ). Vertigo complaint was present in 28 (70%) patients with RA but no individuals in the control group complained of it; the difference between two groups was highly statistically significant ( $P<0.01$ ) (Table 3).

In the present study, we also found that in the RA group, five patients had only impaired smooth pursuit, 11 patients had only impaired saccade, and nine patients had only canal paresis. Four patients had impairment in both smooth pursuit and saccade testing. One patient had impairment in saccade tracing, smooth pursuit, and canal paresis. According to VNG testing, there were central abnormalities in 12 (30%) patients, peripheral abnormalities in nine (22.5%) patients, and mixed abnormalities in one (2.5%) patient.

Ferrara *et al.* [1] reported that electronystagmography (ENG) testing revealed central vestibular disorders in patients with RA, regardless of the stage of disease or the age of the patients. Kakani *et al.* [2] assessed the saccade tracings and bithermal caloric test results of 25 patients with RA and found no abnormalities in the test results. King *et al.* [22] investigated the vestibulo-ocular reflex, optokinetic reflex, and postural function in 20 patients with RA and concluded that RA was not associated with substantial vestibular dysfunction.

Yilmaz *et al.* [10] used smooth pursuit, saccadic movement, positional, and bithermal caloric tests to

evaluate the vestibular system. None of the patients with RA or the controls exhibited spontaneous nystagmus, which indicates that there was no acute vestibular disease. Then, they concluded that vestibular dysfunction in RA could be associated with chronic inflammatory process of the disease. ENG test results suggested central and/or peripheral vestibular dysfunction in 34.7% of the patients with RA, a finding that was statistically significant from the result for controls.

In the present study we found that there was a correlation between impaired pursuit test in patients with RA and duration of RA and RF. This correlation was statistically significant ( $P < 0.05$ ). In addition, there was a correlation between impaired water caloric test in patients with RA and RF and this correlation was a statistically significant ( $P < 0.05$ ). As regards impaired saccade test in patients with RA, there was no correlation between the test and age, sex, duration of RA, laboratory findings, and vertigo complaint (Table 4). In our study, 70% of RA patients experienced dizziness and/or vertigo. There was no association between presence of dizziness and VNG abnormalities (Table 4). This was in agreement with Yilmaz *et al.* [10] who failed to show an association between the presence of vertigo complaint and VNG testing, which could be attributed to gradual involvement of the vestibular system causing labyrinth compensation. Yilmaz *et al.* [10] found that ESR, C-reactive protein, and RF values were slightly increased in patients whose central vestibular test results showed impairment; those differences were not statistically significant.

On the other hand, El-Fatta *et al.* [23] reported central and or peripheral vestibular dysfunctions in 47.7% of the patients with RA, and 51.11% of them experienced dizziness and/or vertigo. There was an association between the presence of dizziness and ENG abnormalities ( $P = 0.03$ ). Moreover, Evereklioglu *et al.* [24] suggested that vertigo complaints were mainly orthostatic and due to general microvascular involvement.

## Conclusion

There is an association between RA and audiovestibular system dysfunction regardless of the clinical and demographic situation of the patients. We assume that the shearing and vestibular disturbance in RA is more prevalent than previously recognized. High-frequency hearing loss in RA patient could be an indicator of cochlear involvement.

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## Conflicts of interest

There are no conflicts of interest.

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