Original Article

Evaluation of Subclinical sensor neural hearing loss prevalent in Rheumatoid Arthritis patients with RA referred to Golestan Hospital of Ahvaz in 2019

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Abstract

Background: Autoimmune inner ear disease (AIED) and the relationship between hearing loss (hearing impairment) and autoimmune diseases were first reported by Brian McCabe in 1979. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that has affected around 1% of the people in the world. Therefore, the purpose of this study is to examine sensorineural hearing loss (SNHL) in patients with RA using high-frequency audiometry (HFA). **Materials and Methods:** This research was an analytical cross-sectional study conducted on patients with RA referred to Golestan Hospital of Ahvaz in 2019. The patient group was included patients with a positive RA test referred to the rheumatology clinic of Golestan hospital of Ahvaz. IBM SPSS Statistics 25 was used for statistical analyses. Data were analyzed through descriptive statistics including mean, standard deviation (SD), frequency and frequency percentage**. Results:** Of a total of 60 patients examined, 28 (46.7%) were male and 32 (53.3%) were female.The auditory threshold in the patient group was significantly higher at frequencies of 500, 1000, 10,000, 14,000 and 16,000 Hz. The relationship between hearing loss (at frequencies from 250 to 8,000 Hz) and Rheumatoid factor (RF) autoantibody was also examined in the patient group. Of patients with hearing loss, 92.3% had this antibody whilst the remaining 7.7% of patients had no antibody. **Conclusion**: According to the foregoing observations and discussions, hearing loss should be regarded as an influential disorder in R.A And patients with hearing loss (especially those with positive anti-CCP and RF antibody tests) need to undergo the necessary audiometry examinations (especially high-frequency audiometry, if possible) before the incidence of severe and clinical hearing loss, to identify them at the subclinical stage and guide them to take the necessary measures.

Keywords: Rheumatoid Arthritis, hearing loss, sensorineural

Introduction

Autoimmune inner ear disease (AIED) and the relationship between hearing loss (hearing impairment) and autoimmune diseases were first reported by Dr. Brian McCabe in 1979. Such a hearing loss was defined in a group of patients with progressive bilateral SNHL and changes in the immunological tests in response to immunosuppressive therapy [1, 2]. Following this report, other studies showed that the inner (internal) ear is prone to an autoimmune response and SNHL can occur due to various autoimmune diseases including rheumatoid arthritis (RA) [3, 4]. The first case of hearing loss in patients with RA was reported around 50 years ago by Copeman (1963) [5]. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that has affected around 1% of the people in the world [4, 6]. The disease is characterized by the inflammation of the synovial membranes of the diarthrodial joints [7]. The disease initially affects the small joints of hand and foot and causing joint damage and physical disability as well as extensive systemic involvements when the disease is progressed [8, 9]. The prevalence of RA raises with age and is more common in women [10]. RA is associated with progressive disability, multiple systemic complications, premature death, and considerable socioeconomic costs [11]. Extra articular involvement is another characteristic of RA that affects various systems and organs of the body including the heart, lungs, skin, and eyes [4, 11]. Also, the temporomandibular joint, cervical spine, larynx, and inner ear in the head and neck area can be involved [10, 12]. According to some studies, this disease can also cause SNHL through an immune-mediated

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mechanism [13-15]. Hearing loss in patients with RA can be sensorineural (SNHL), conductive (conductive hearing loss - CHL), or mixed (mixed hearing loss - MHL) [7]. SNHL is the most prevalent hearing disorder in patients with RA, which is reported in 25% to 75% of these patients, whilst the prevalence of CHL and MHL is reported to be lower [7, 16-18].The pathogenesis of hearing loss in RA is still unknown, although it may be associated with vasculitis, neuritis, autotoxicity and/or an immunological disorder [3, 19, 20]. RA can affect the hearing through different mechanisms. First, it may act as inflammatory arthritis and directly affect the two incudostapedial (ISJ) and incudomalleolar (IMJ) synovial joints of the middle ear and cause CHL. Second, extraarticular involvements (vasculitis and mononeuritis) may affect the cochlea and the cochlear nerve and cause a true auditory neuropathy (AN) and consequently a decrease in sensorineural hearing. Third, the autoimmune mechanism can cause destructive inflammation of the cochlear hair cells and hence the hearing loss can result from the direct immune response of T and B lymphocytes (T and B Cells) to the inner ear proteins. Fourth, some of the medications prescribed to treat RA can affect the ear. These include salicylates and other Nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial medications, and some other disease regulating agents [18-22]. Therefore, hearing loss may be a systemic representation of vascular involvement in patients with RA and may significantly affect patient health. However, the risk associated with the incidence of hearing loss in patients has not been exactly known [18]. Also, the characteristics of hearing loss in these patients are not entirely recognized [7, 17]. Although the relationship between RA and hearing loss as well as the greater prevalence of hearing loss in patients with RA (as compared with healthy people) has been reported in multiple studies [4, 7, 18], the results of a study show that there is no significant difference in auditory threshold between patients with RA and healthy people [23]. Therefore, the relationship between RA and hearing loss still is controversial and needs further investigation with regulating potential risk factors. Various parameters such as age, gender, obesity, duration of illness, noise exposure, smoking and alcohol consumption, education, cardiovascular risk factors, and medications prescribed may affect hearing loss [7, 24-26]. According to various studies, SNHL should be considered in clinical examinations of patients with RA due to the potential relationship between RA and hearing loss [3]. High-frequency SNHL is extremely prevalent in patients with RA and this disorder can be initially diagnosed using high-frequency audiometry (HFA) [27]. A recent study showed that HFA (as compared with PTA - Pure-tone audiometry) can detect more cases of hearing loss in patients with RA [3]. Therefore, the purpose of this study is to examine SNHL in patients with RA using HFA.

Material and Methods

This was an analytical cross-sectional study conducted on patients with RA referred to Golestan Hospital of Ahvaz in 2019. The patient group was included patients with a positive RA test referred to the rheumatology clinic of Golestan hospital of Ahvaz. The pre-implementation study was approved by the University's Ethics Committee The control group was included healthy people with no history of ear disorders, exposure to noise, consumption of ototoxic medications, or a history of hearing loss in the family. HFA thresholds (0.25, 0.5, 1, 2, 4, 8, 10, 12, 14 and 16 kHz) were measured for all patients and healthy controls. The threshold was defined as the least level of intensity (in dB) in which the participant under examination responds to at least 50% of the sound presentations. Hearing loss was defined as a 15 dB increase in the auditory thresholds at frequencies from 250 to 8,000 Hz. The frequency of hearing loss in audiometry was calculated with a confidence interval (CI) of 95%, according to a 15 dB increase in the auditory thresholds at frequencies from 250 to 8,000 Hz used for statistical analyses

Data analysis

Data were analyzed by version 25, SPSS software and parametric tests were used for normal data and nonparametric tests were used for abnormal data. The meaning has described with P-value less than 0.05.

Ethical issue

It is certified that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Informed written consent was obtained from all participants and the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences approved this study at 2015. The study protocol conforms to the ethical guidelines of the 2008 Declaration of Helsinki. Ethical code of this thesis: **"IR.AJUMS.REC.1398.396"**

Results

This was an analytical cross-sectional study conducted on patients with RA referred to Golestan Hospital of Ahvaz, where a group of healthy and volunteer people was considered as the control group. The patient and control groups were included in the study following inclusion and exclusion criteria and then underwent audiometry examinations. Of a total of 60 patients examined, 28 (46.7%) were male and 32 (53.3%) were female. Of all 28 men, 13 were in the patient group and 15 in the control group. Of all 32 women, 17 were in the patient group and 15 in the control group (Table 1; Fig. 1). Participants ranged from 27 to 61 years old (41.6 years in mean) in the patient group and 28 to 56 years old (41.23 in mean) in the control group. The majority of participants in both groups ranged from 36 to 55 years old (Table 2; Fig..2). The mean auditory threshold was compared between the two groups at frequencies of 250, 500, 1,000, 2,000, 4,000, 8,000, 10,000, 12,000, 14,000 and 16,000 Hz. The auditory threshold in the patient group was significantly higher at the frequencies of 500, 1,000, 10,000, 14,000 and 16,000 according to examinations and the T-test results ($p<0.05$) (Table 3). The mean auditory threshold at frequencies of 250 to 8,000 Hz was compared between the patient and control groups. The mean value was respectively

17.5 and 12.1 in the patient and control groups. The auditory threshold was significantly higher at the above frequencies in the patient group than in the control group, according to the T-test results ($p<0.05$) (Table 4). The mean auditory threshold at frequencies of 10,000 to 16,000 Hz was compared between the patient and control groups. The mean value was respectively 30.08 and 24.5 in the patient and control groups. The auditory threshold was significantly higher at the above frequencies in the patient group than in the control group, according to the T-test results ($p<0.05$) (Table 5). The mean auditory threshold at frequencies of 250 to 8,000 Hz (A) and 10,000 to 16,000 Hz (B) were compared within the patient group. The mean value was respectively 17.59 and 30.34 in the A and B subgroups. The auditory threshold was significantly higher at frequencies from 10,000 to 16,000, according to the one-sample T-test results ($p<0.05$) (Table 6). The frequency of hearing loss at 250 to 800 Hz with a cut-off point of 15 dB was compared between the two groups. Hearing loss was 43.3% in the patient group whilst there was no hearing loss in the control group. Therefore, Fisher's exact test results revealed that the frequency of hearing loss is significantly higher in the patient group than the control group ($p<0.05$) (Table 7; Fig. 3). The relationship between mean auditory thresholds at frequencies of 500, 1,000 and 2,000 and age in the patient group was not significant, according to the ANOVA results ($p<0.05$) (Table 8; Fig. 4). The relationship between mean auditory thresholds at frequencies of 500, 1,000 and 2,000 and duration of disease in the patient group was also not significant, according to the ANOVA results ($p<0.05$) (Table 9; Fig. 5). The relationship between the hearing loss at 250 to 8,000 HZ and the level of anti-CCP antibody was investigated in the patient group. Of patients with hearing loss, 69.2% had this antibody and the remaining 30.8% had no such antibody. Therefore, Fisher's exact test results confirmed that the level of anti-CCP antibody is significantly associated with hearing loss in these patients ($p<0.05$) (Table 10; Fig. 6). The relationship between the hearing loss at 250 to 8,000 HZ and the level of RF antibody was investigated in the patient group. Of patients with hearing loss, 92.3% had this antibody and the remaining 7.7% had no such antibody. Therefore, Fisher's exact test results confirmed that the level of RF antibody is significantly associated with hearing loss in these patients ($p<0.05$) (Table 11; Fig. 7). The relationship between the hearing loss at 250 to 8,000 HZ and gender was investigated in the patient group. Of patients with hearing loss, 25% were male and 18.8% were female. Therefore, Fisher's exact test results confirmed that there is no significant relationship between gender and hearing loss in these patients ($p<0.05$) (Table 12; Fig. 8).

Discussion

As mentioned in the previous chapter, the frequency of subclinical hearing loss was significantly higher in patients with RA than in healthy controls. To reach a more accurate examination, six frequencies at normal audiometry and four frequencies at high-frequency audiometry (HFA) were tested in the patient and control groups.

According to the results, the rate of subclinical hearing loss at both frequencies was higher in the patient group. Of six frequencies at normal audiometric, a significant hearing loss was only observed at two frequencies, whilst a significant hearing loss was observed at three (out of four) HFAs. Therefore, the incidence of subclinical hearing loss in patients with RA initially occurs at high frequencies, as confirmed by comparing the mean thresholds of these two frequency ranges in the patient group.

As with other RA complications, where the association of anti-CCP and RF antibodies may indicate the severity of the disease, the association of these two antibodies with subclinical hearing loss was also significant, whilst no considerable relationship was observed with age, gender, and duration of disease. Through the literature review, the strengths and weaknesses of this research can be identified. The application of high-frequency audiometry (HFA) is one of the strengths of this study because few researchers have used the frequencies of 10,000 to 16,000 Hz to monitor patients. The comparison of auditory thresholds in the two groups at 10 different frequencies is another strength of this study because the majority of studies have been conducted only using 4 to 6 frequencies. The mean auditory threshold at each frequency was separately calculated for the patient and control groups and compared and the corresponding statistical tests and comparisons were performed for each frequency, whilst such a separation is less apparent in previous studies. As with other studies, there was no significant relationship between the incidence of hearing loss and age, gender, and duration of disease. Participants of the patient and control groups have also ranged from 20 to 50 years old in the previous cross-sectional studies. Excluding the duration of disease when selecting patients is one of the disadvantages of this study compared to other studies, which restricted us to examine the relationship between hearing loss and duration of disease in this study.

Research limitations

Since the early diagnosis of hearing loss before the incidence of severe and visible hearing loss in patients with AR was one of the primary objectives of this study, therefore, patients had to be selected from those who have no complaints of hearing loss. One of the serious problems in conducting this study was, therefore, justification of patients to examine the auditory system and obtain patient consent form as well as to guide them on how to attend the audiometry center on time and cooperate during testing. Despite sufficient justification and obtaining consent form, many patients, unfortunately, refused to perform the audiometry, which eventually led us to introduce alternatives.

Conclusion

According to the foregoing observations and discussions, hearing loss should be regarded as an influential disorder in RA. And patients with hearing loss (especially those with positive anti-CCP and RF antibody tests) need to undergo the necessary audiometry examinations (especially HFA, if

possible) before the incidence of severe and clinical hearing loss, to identify them at the subclinical stage and guide them to take the necessary measures.

Recommendations

Given the limited number of participants in most studies conducted in Iran and abroad, designing (and conducting) a jointly study at a much larger scale in collaboration with other Iranian academic centers, considering more variables, especially medications, duration of disease, the severity of the disease, and other complications is recommended to offer further benefits to patients. Regarding the importance of the hearing loss, providing patients with necessary educational instruments in rheumatology clinics to inform patients of these complications and encourage them to take preventive measures is also recommended.

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Disclosure of interest.

The authors report no conflicts of interest.

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Table 1: Frequency distribution by gender

	total	control	patients
male	28	15	13
	46.7%	50.0%	43.3%
female	32	15	17
	53.3%	50.0%	56.7%
total	60	30	30
	100.0%	100.0%	100.0%

Table 2: Frequency Distribution by age

Age	Total	control	patients
25-35	20	9	11
	33.3%	30.0%	36.7%
36-45	16	10	6
	26.7%	33.3%	20.0%
46-55	20	8	12
	33.3%	26.7%	40.0%
+55	4	3	1
	6.7%	10.0%	3.3%
Total	60	30	30
	100.0%	100.0%	100.0%

Table 3: Comparison of mean hearing thresholds for each frequency in the two patient and control groups

Hearing thresholds	P-value	Degrees of freedom	T	Standard error	SD	mean	number	Group
250	.611	58	.512	.67381	3.69062	14.0000	30	AR
				.35423	1.94020	11.1667	30	Control
500	.000	58	3.722	2.14065	11.72481	20.1667	30	AR
				.33369	1.82771	11.2500	30	Control
1000	.000	58	4.116	1.20275	6.58771	16.0833	30	AR
				.44014	2.41076	10.0833	30	Control
2000	.083	58	1.764	1.76227	9.65236	19.2500	30	AR
				.46321	2.53708	9.8333	30	Control
4000	.059	58	1.924	.76830	4.20813	10.4167	30	AR
				.26803	1.46805	10.0000	30	Control
8000	.053	58	1.974	2.71737	14.88365	25.6667	30	AR
				.80349	4.40089	20.6667	30	Control
10000	.040	58	2.106	3.23457	17.71649	30.2833	30	AR
				.69567	3.81034	23.9167	30	Control
120000	.053	58	1.974	3.36351	18.42272	35.5000	30	AR
				.81942	4.48817	28.6667	30	Control
140000	.040	58	2.106	3.44778	18.88429	42.7500	30	AR
				1.33087	7.28950	34.9667	30	Control
160000	.000	58	4.191	.94474	5.17456	14.8611	30	AR
				.20946	1.14728	10.8056	30	Control

Table 4: Comparison of the mean thresholds between the control and patient groups at frequencies from 250 to 8,000 Hz

Hz	P-value	Degrees of freedom	T	Standard error	SD	mean	number	Group
250-8000	.000	58	4.24	1.25600	6.87940	17.5972	30	AR
				.24662	1.35082	12.1667	30	Control

Table 5: Comparison of the mean hearing thresholds between the control and patient groups at frequencies from 10,000 to 16,000 Hz

Hz	P-value	Degrees of freedom	T	Standard error	SD	mean	number	Group
10000-16000	017/0	58	2.45	2.49606	13.67146	30.8486	30	AR
				.49249	2.69749	24.5889	30	Control

Table 6: Comparison of the mean hearing thresholds in the patient group between frequencies from 250 to 8,000 Hz and 10,000 to 16,000

Hz	P-value	Degrees of freedom	T	Standard error	SD	mean	number
250-8000	.000	29	14.011	1.25600	6.87940	17.5972	30
10000-16000	.000	29	12.359	2.49606	13.67146	30.8486	30

Table 7: Frequency of hearing loss at frequencies from 250 to 8,000 Hz between the two patient and control groups

group	total	control	patients
Can hear	47	30	17
	78.3%	100.0%	56.7%
hearing impaired	13	0	13
	21.7%	.0%	43.3%
Total	60	30	30
	100.0%	100.0%	100.0%

*Statistical result: Value= 16.59 df= 1 sig=0/0000

Table 8: Descriptive statistics; mean frequencies at 500, 1,000 and 2,000 Hz by age

Group(age)	number	mean	SD	Standard error
25-35	20	14.5833	8.47899	1.89596
36-45	16	11.9792	4.59342	1.14836
46-55	20	16.0000	7.54422	1.68694
+55	4	15.8333	9.64653	4.82327
total	60	14.4444	7.36087	.95028

Table 9: The relationship between the duration of disease and the mean frequencies at 500, 1,000, and 2,000

Duration of illness (year)	number	mean	SD	Standard error
1	4	12.2917	3.21851	1.60925
2	1	34.1667	.	.

3	2	18.7500	10.01735	7.08333
4	2	17.5000	7.07107	5.00000
5	2	16.6667	11.78511	8.33333
6	4	13.7500	1.98373	.99187
7	5	19.3333	8.15220	3.64577
8	2	17.9167	6.48181	4.58333
9	2	19.1667	10.60660	7.50000
10	1	26.6667	.	.
11	1	9.1667	.	.
13	1	29.1667	.	.
15	1	7.5000	.	.
16	1	30.0000	.	.
24	1	37.5000	.	.
total	30	18.5000	8.58639	1.56765

Table 10: Comparison of hearing loss with the anti-CCP antibody at frequencies from 250 to 8,000 Hz

	hearing impaired	Can hear	total
Positive	9	5	14
	69.2%	29.4%	46.7%
Negative	4	12	16
	30.8%	70.6%	53.3%
total	13	17	30
	100.0%	100.0%	100.0%

*Statistical result: Value= 4.69 df= 1 sig=0/030

Table 11: Comparison of hearing loss with the RF antibody at frequencies from 250 to 8,000 Hz

	Hearing impaired	**Can hear**	**total**
Positive	12	21	9
	92.3%	70.0%	52.9%
negative	1	9	8
	7.7%	30.0%	47.1%
total	13	30	17
	100.0%	100.0%	100.0%

*Statistical result: Value= 5.43 df= 1 sig=0/020

Table 12: Comparison of hearing loss with gender at frequencies from 250 to 8,000 Hz

	female	Male	total
Can hear	26	21	47
	81.3%	75.0%	78.3%
Hearing impaired	6	7	13
	18.8%	25.0%	21.7%
total	32	28	60
	100.0%	100.0%	100.0%

*Statistical result: Value= 344/0 df= 1 sig=0/558

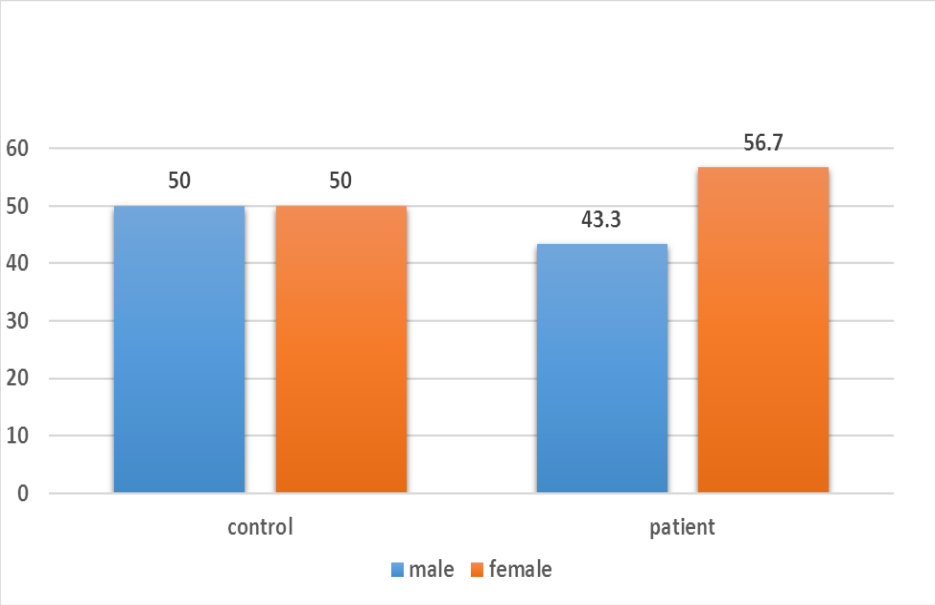

Fig. 1: Distribution of gender frequency in patient and control groups

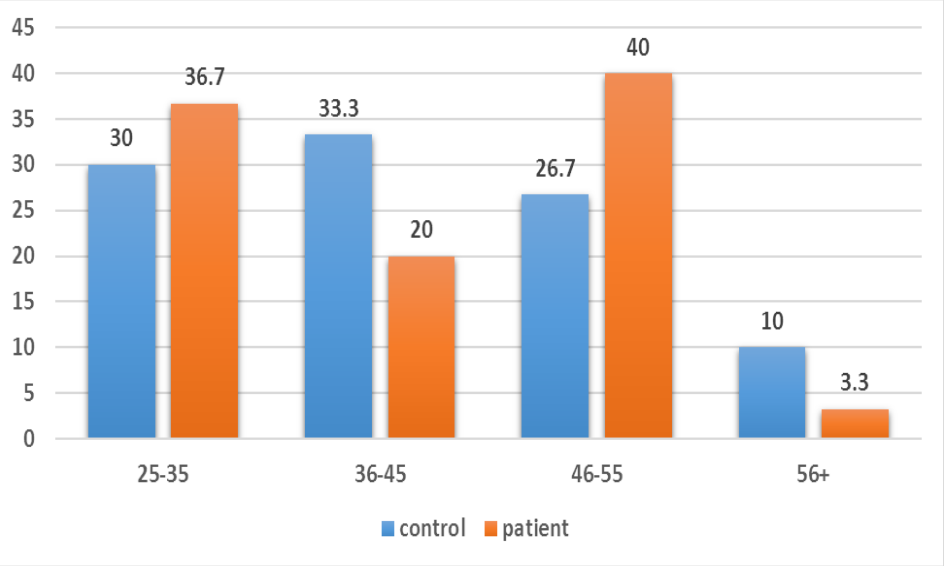

Fig. 2: Distribution of age frequency in patient and control groups

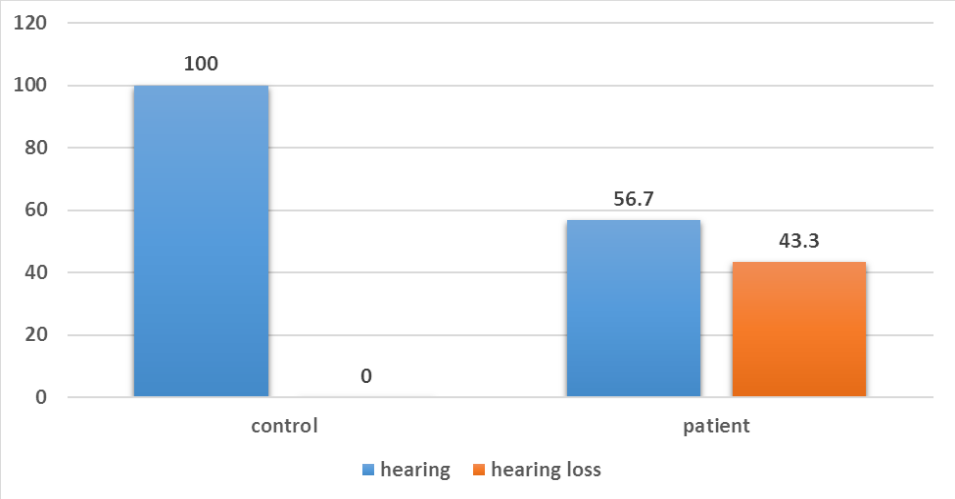

Fig. 3: Frequency of hearing loss in patient and control groups

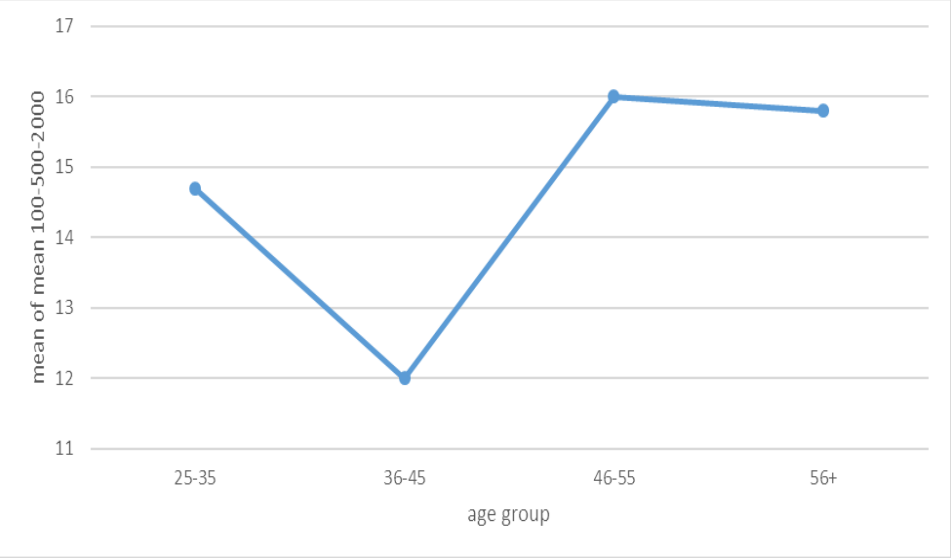

Fig. 4: Descriptive statistics; mean frequencies at 100, 500, and 2000 Hz by age

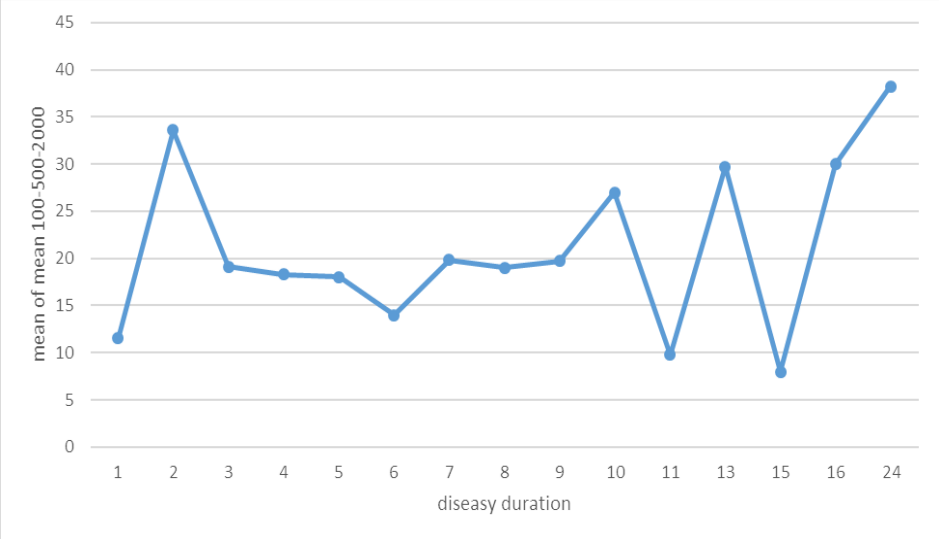

Fig. 5: Mean frequencies at 100, 500, and 2000 Hz by the duration of disease

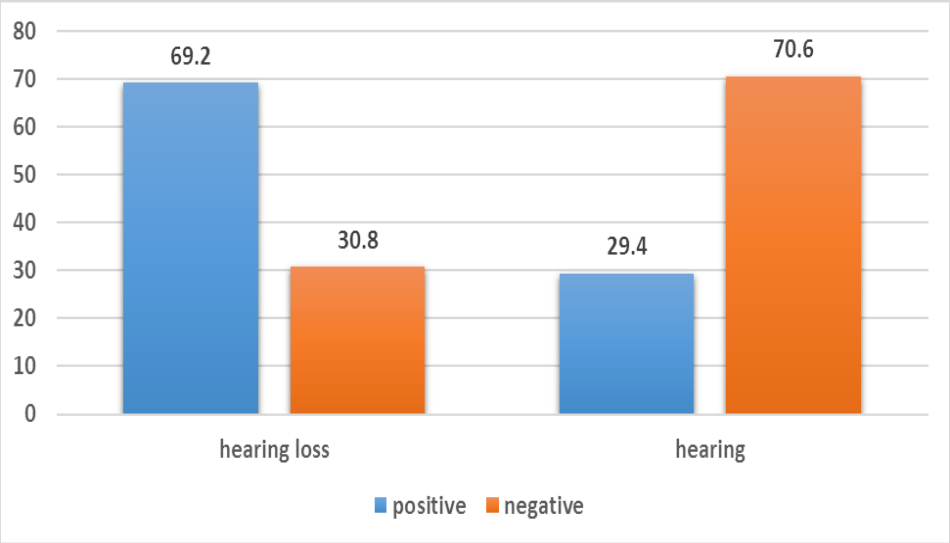

Fig. 6: The relationship between the frequency of hearing loss and anti-CCP antibody

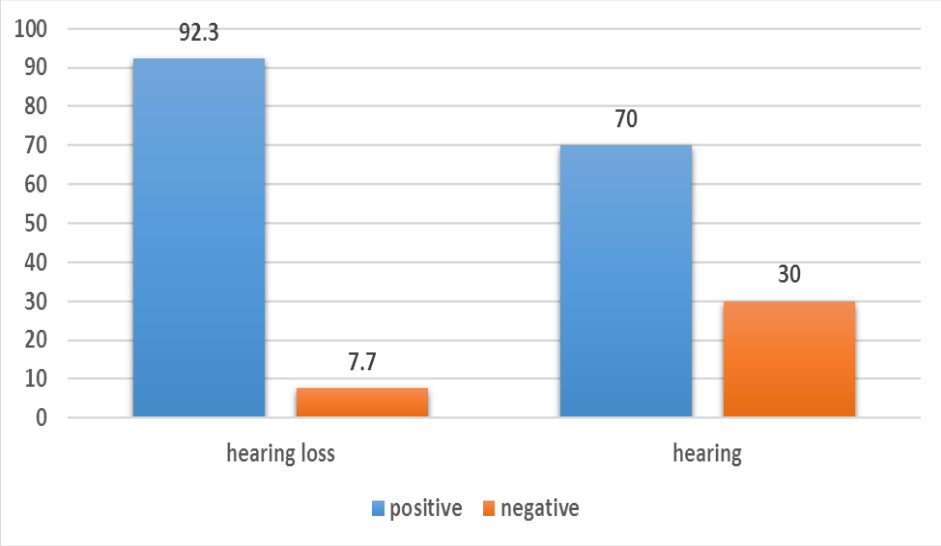

Fig. 7: The relationship between the frequency of hearing loss and RF antibody

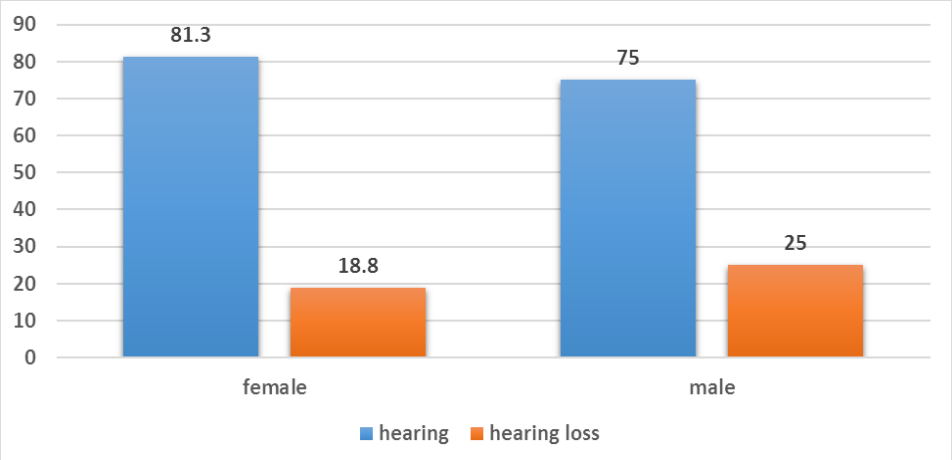

Fig. 8: The relationship between hearing loss and gender