■ ORIGINAL ARTICLE

Hearing Impairment in Patients With Rheumatoid Arthritis

Francisco Javier García Callejo, Noemí Conill Tobías, Noelia Muñoz Fernández, Carlos de Paula Vernetta, Ignacio Alonso Castañeira, and Jaime Marco Algarra
Servicio de Otorrinolaringología, Hospital Clínico Universitario de Valencia, Universidad de Valencia, Valencia, Spain

Objective: To evaluate the characteristics of hearing loss (HL) in patients with rheumatoid arthritis (RA).
Patients and method: A comparative case-control study was performed with 194 patients and 107 healthy subjects.
All of them were submitted to pure-tone audiometry and detection of inflammatory parameters and Western blot for anticochlear antibodies.
Results: HL was detected in 42.7% of patients with RA (15.9% in controls; *P*<.001). This was sensorineural in 38.6%. Three or more altered blood parameters appeared in 28.9% of patients with RA (17.6% in controls; *P*<.01).
We observed positive Western blot in 12% of patients with RA and HL and none among healthy controls.
Conclusions: There is a predisposition to HL, mainly sensorineural, in RA. In view of this prevalence, audiologic reviews must be performed to try to determine if this disorder shows an immunomediated aspect so that a therapeutic alternative could modify the course of HL.

Key words: Hearing loss. Rheumatoid arthritis. Pure-tone audiometry.

Deterioro auditivo en pacientes con artritis reumatoide
Objetivo: Valorar la relación de la hipoacusia con la artritis reumatoide (AR).
Pacientes y método: Estudio comparativo de casos y controles equiparados en edad y sexo, de 194 pacientes con AR y 107 sujetos sanos. Se efectuó en todos valoración mediante audiometría tonal y determinación de parámetros inflamatorios y *Western blot* de anticuerpos anticocleares.
Resultados: El 42,7 % de los pacientes con AR presentaron hipoacusia (el 15,9 % de los controles; p < 0,001). En el 38,6 % de ellos fue neurosensorial. El 28,9 % de los casos presentaron 3 o más parámetros alterados (el 17,6 % de los controles; p < 0,01). El 12 % de los sujetos con AR e hipoacusia tuvieron un *Western blot* positivo. No se detectó ninguno en los controles.
Conclusiones: Hay una predisposición a la hipoacusia en los sujetos con AR, principalmente neurosensorial. Esta prevalencia obliga a la revisión audiológica de este grupo e intentar definir si este trastorno tiene un componente inmunomediado que permitiera un tratamiento modificador del curso de la hipoacusia.

Palabras clave: Hipoacusia. Artritis reumatoide. Audiometría tonal.

INTRODUCTION

Rheumatoid arthritis (RA) is a clinical entity characterized by disseminated erosive arthropathy and various systemic inflammatory manifestations.[1] Of unknown origin, there are immunomediation markers in peripheral blood that are not necessary to detect the illness but highly indicative for its suspicion. Thus, diagnosis involves clinical, radiological, and laboratory findings.[2,3]

The involvement of other organs is well-known. However, the hearing of patients affected by RA is not usually a reason for them to see a doctor nor grounds for alert, probably because it does not imply a life-threatening condition for their chronobiological development. As it is a disorder with a high involvement of the immune function, whether humoral (high rheumatoid factor titres (RF), interleukin 2, interferon gamma, lymphocyte migration inhibiting factors and macrophage inhibiting factors, and monocyte chemotaxis inhibitors) or cellular (activation of polyclonal B and Th in response to antigen presenting cells), the laboratory profile coincides with that often described in auto-immune hearing losses: hypocomplementaemia, hypergammaglobulinaemia, leukocytosis, positive results for auto-antibodies, and increased globular sedimentation velocity (GSV) as well as acute phase reagents.[4]

Nonetheless, we have observed that the patients affected often present slow-coursing hypoacusia, only reviewed in the face of a subjective impression of hearing loss expressed by the patient in person. Thus, this paper has been designed

Correspondence: Dr. F.J. García Callejo.
Luis Oliag, 71, 8. 46006 Valencia. España.
E-mail: jgarciacall@hotmail.com

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to review the audiological characteristics of patients with RA and correlate the parameters defining this illness with any potential hypoacusia they show, so as to identify connections or prognostic factors to allow this auditory impairment to be foreseen.

PATIENTS AND METHOD

Study Groups

The recruitment period extended from July, 1994, to June, 2006. During this time, hypoacusic and normoacusic patients were assessed, as part of a longitudinal, prospective, descriptive and interventionist revision, in the context of 2 clearly defined samples:

- Patients diagnosed as having RA in accordance with the conditions stipulated by the American College of Rheumatology in 1988, which requires them to meet 4 of the following 7 criteria: *a)* rigidity of joints in the early morning lasting for more than 1 hour and at least 6 weeks; *b)* arthritis of more than 3 joint areas for at least 6 weeks; *c)* arthritis of the hands with swelling for at least weeks; *d)* symmetrical bouts of arthritis for at least 6 weeks; *e)* subcutaneous nodes; *f)* seropositive result for RF, and *g)* radiological alterations in the hands and wrists with erosions or decalcification (n=194). The mean age was 40.3 (9.6) years, with a ratio of men:women of 0.38.
- Control group of healthy subjects without any personal or family history of pathological interest and not receiving any maintenance therapy, recruited in parallel with the other group in an attempt to match the distribution by age and gender (n=107). The mean age was 46.7 (11.2) years, with a ratio of men:women of 0.38.

All of the individuals belonging to both groups were studied using tonal threshold audiometry for 7 frequencies, calculating the percentage of binaural auditory loss in accordance with the legislation in force in Spain.[5]

Both the patients in the case group and those in the control group were previously informed of the intention of the tests carried out and they each gave written consent.

Exclusion Criteria

The following were the study's exclusion conditions:

- Activity in social or work-related environments with acoustic contamination in excess of 85 dB HL or with acoustic peaks in excess of 140 dB HL.
- Exposure to agents with an acknowledged ototoxic effect for at least 10 days during the preceding 2 months or for 30 days in the 6 months prior to the study, with special emphasis on the occasional consumption of aspirin, hydroxychloroquine, or gold salts.
- Exposure to agents with an acknowledged immunomodulator effect in the 30 days prior to the study, including: glucocorticoids, methotrexate, leflunomide, cyclosporin, azathioprine, chlorambucil, cyclofosfamide, and interferons.
- Having suffered, in the 60 days prior to the study, any acute or sub-acute process that could be resolved by appropriate therapeutic procedures. When this occurred, the performance of the tests was postponed to a later time.
- A previously known diagnosis of a chronic condition or surgery of the middle ear: adhesive process, otosclerosis, perforation of the ear drum, cholesteatomatous otitis.
- Not being able to complete any of the laboratory tests effected at the same time as the hearing study.
- Having been studied prior to this monitoring, even where the audiological characteristics or the underlying illness had changed.

The following shall not be considered exclusion factors:

- The concomitant coursing of another chronic, infectious, immunomediated, tumoral, or metabolic condition, except for the chronic otitis media situations mentioned above, which always implied the rejection of the patient from this study.
- Concomitant vestibular symptoms.
- Ototoxic or immunomediation therapies when these were administered outwith the time windows required in the exclusion criteria.

Peripheral Blood Analysis

Both the cases and the controls were subjected to a screening battery of laboratory tests (SB), which included the following parameters obtained in peripheral blood by means of a puncture in the cubital vein: GSV, total concentrations of immunoglobulins IgM, IgG, and IgA, fibrinogen, C-reactive protein (CRP), ASLO titres, IgM, IgG, and IgA fractions of RF, C3 and C4 complement factors, CH50 haemolytic activity, leukocytosis, and lymphocytosis absolute counts and ratio of T4/T8 sub-populations. A battery was considered to be positive if 3 or more parameters indicated an excess or defect with respect to their reference values.

Similarly, a serum sample was obtained from both groups for the study of specific auto-antibodies against bovine cochlear antigen by means of a Western blot (WB) test. The treatment of the antigenic extracts followed the design of Moscicki et al[6] from 1994. Electrophoresis of the cells loaded in polyacrylamide gels was adjusted to Laemmli's method[7] and the transfer of the electrophoretic profile to a solid water-repellent base was effected in accordance with the description of Barnette.[8] Any identification of a migration band through enzyme immunoanalysis was considered positive.

Clinical Characteristics of the Illness

In addition to the markers obtained in blood (of particular interest in the determinations of GSV and CRP), in the group of patients with RA, at the same time as the audiometric study results, a note was taken of the parameters habitually classifying the illness and allowing their clinical monitoring and any possible response to treatment. These parameters were recorded by a specialist in rheumatology and included:

– Age and gender of the patient.
– Time elapsed since the diagnosis of RA until the moment of the study.
– Health assessment questionnaire (HAQ) on the patient's functional capacity, assessing the limitations to carry out various activities grouped into 8 areas. Each area receives a score from 0 (without difficulty) to 3 (maximum disability). The value of the HAQ is expressed in the number of points obtained (maximum of 24) divided by the 8 areas proposed. Therefore, its value ranges from 0 to 3.
– The Ritchie Index (RI), or number of painful joints in the 44 analyzed, as reported by the patient.
– Number of swollen joints (NSJ), as examined by the specialist, of the 44 analyzed.
– Analogue visual scale (AVS) for pain in general, as reported by the patient, where 0 expresses total normality and 10, the most unbearable pain.
– Disease Activity Score (DAS Index), obtained by the mathematical calculation of the parameters indicated above according to the following formula:

$$DAS = 0.54(RI) + 0.065(NSJ) + 0.33(\ln GSV) + 0.0072(AVS)$$

The result of the DAS Index desired for a patient with RA lies between 1.2 and 2.4. Values >3.7 were considered to be an unsatisfactory progression of the disease.

Statistical Processing

The comparison between an observed and a theoretical mean was effected between the case-control groups using the Student-Fisher *t* test, assuming that the sample distribution of the means follows a standard norm. For qualitative characteristics of the two populations expressed as percentages, the conformity test used for comparisons was χ^2. In both cases, statistical significance was deemed to exist when $P<.001$. The linear association between two quantitative variables was assessed using the R correlation coefficient through the formulation of straight-line regression equations. This system was provided by the SPSS statistical application.

RESULTS

The airway values for each frequency were noted in 388 ears belonging to subjects diagnosed as having RA and in 214 ears from members of the control group.

The mean values of the thresholds obtained for each frequency were always significantly higher in patients with RA than in healthy controls. In addition, pursuant to the current legislation classifying hearing loss by measuring thresholds at 500, 1000, 2000, and 3000 Hertz, this was detected in 42.7% of subjects with RA and quantified hypoacusia, versus 15.9% observed among the controls, a difference that was also statistically significant.

The hearing loss recorded in the 2 groups was mainly sensorineural. Only 4% of the patients with RA showed any transmission factor in the audiometric examination performed. In addition, the screening battery showed many more alterations in the parameters for the case group and only in this group was it possible to observe a small number of patients with antibody bands in the WB test (Table 1).

Of the 83 cases with RA in whom hypoacusia was detected, 71.1% were female, versus 41.2% of the 17 controls in whom it was noted. Comparing the hearing

Table 1. Audiometric Characteristics of the Case and Control Groups*

	Cases With RA (n=194; 388 Ears)	*Healthy Controls (n=107; 214 Ears)*
Airway threshold at 250 Hz	17.7 (11.7) dB HL	14.3 (10.8) dB HL†
Threshold at 500 Hz	21.3 (11.0) dB HL	15.5 (10.1) dB HL†
Threshold at 1000 Hz	23.3 (13.4) dB HL	18.9 (11.9) dB HL†
Threshold at 2000 Hz	30.0 (18.0) dB HL	23.1 (12.7) dB HL†
Threshold at 3000 Hz	36.8 (20.5) dB HL	27.0 (14.9) dB HL†
Threshold at 4000 Hz	42.2 (22.0) dB HL	29.0 (15.8) dB HL†
Threshold at 8000 Hz	43.0 (19.0) dB HL	34.6 (17.3) dB HL†
Σ 4 conversational tones	111.7 (55.6) dB HL	84.6 (45.7) dB HL†
Patients with SB+	45 (23.2%)	5 (4.7%)†
Patients with WB+	11 (5.7%)	0 (0%)†
Patients with hypoacusia	83 (42.7%)	17 (15.9%)†
Conductive hypoacusia	3 (1.5%)	5 (4.7%)
Mixed hypoacusia	5 (2.5%)	0 (0%)
Sensorineural hypoacusia	75 (38.6%)	12 (11.2%)†

*All of the tones showed a significantly higher mean airway threshold in the subjects with RA. In the group with RA, a significantly high number of individuals was also seen to have alterations in 3 or more parameters in the screening battery (SB) and a positive Western blot (WB) result for anti-cochlear antibodies.
†$P<.001$.

Table 2. Comparative Analysis of the Subjects With Hypoacusia and With or Without Rheumatoid Arthritis*

	Hypoacusias in RA Group (n=83)	*Hypoacusias in Control Group (n=17)*
Females	59 (71.1%)	7 (41.2%)†
Age, mean (SD), y	40.6 (9.2)	51.8 (8.3)‡
Mean hearing loss	24.6% (12.4)	25.2% (13.1)
Patients with SB +	24 (28.9%)	3 (17.6%)†
Alterations in SB/patient	2.2 (1.2)	1.5 (1.0)
Patients with WB +	10 (12.0%)	0 (0%)†
Patients with hearing recovery	10 (12.0%)	0 (0%)†

*Patients with rheumatoid arthritis (RA) were younger and predominantly female. Both the screening battery (SB) and the results of the Western blot (WB) were more markedly positive among the subjects with RA, with statistical significance. The percentage of binaural hearing loss was similar.
†P<0.01.
‡P<0.001.

loss between cases and controls, it was possible to see that the age at which this was recorded was significantly lower among the case group with RA (Table 2). This loss was similar in percentage terms for both groups and the audiometric graph showed an increase in the mean thresholds of the airways mainly in high tones (Figure 1). Among those with hypoacusia, patients with RA presented a greater volume of alterations in the parameters measured in the screening battery (SB) than the individuals in the control group. Furthermore, in 10 cases with RA, a positive WB result was observed versus the absence of positive registers among the control subjects. It must be added that these cases with positive detection of anti-cochlear antibodies were those in which the immunomodulator treatment for the disease at some point in its course (9 cases were treated with corticosteroids and one with methotrexate) constrained the functional recovery of hearing.

From an isolated assessment of the 194 patients with RA, separating them depending on whether or not they presented hypoacusia, it was possible to obtain further data. Neither the mean age nor the mean duration of the disease showed any differences of note. Nonetheless, the percentage of patients with both SB and WB positive was significantly greater in the sub-group of patients with hypoacusia than in those with no hearing loss. Despite this, the volume of patients with positive RF and the mean value of the GSV did not reflect statistically significant differences, although always with a greater tendency towards a deviation from normality among those with hypoacusia.

Clinically speaking, the RA affecting patients with related hypoacusia presented lower HAQ functional disability indices and AVS pain assessment than in the cases of RA without hypoacusia, although the mean number swollen and painful joints was greater among the subjects with hearing loss. The DAS disease activity score was, in short, higher in cases of RA with hypoacusia, although this parameter was not statistical significant (Table 3).

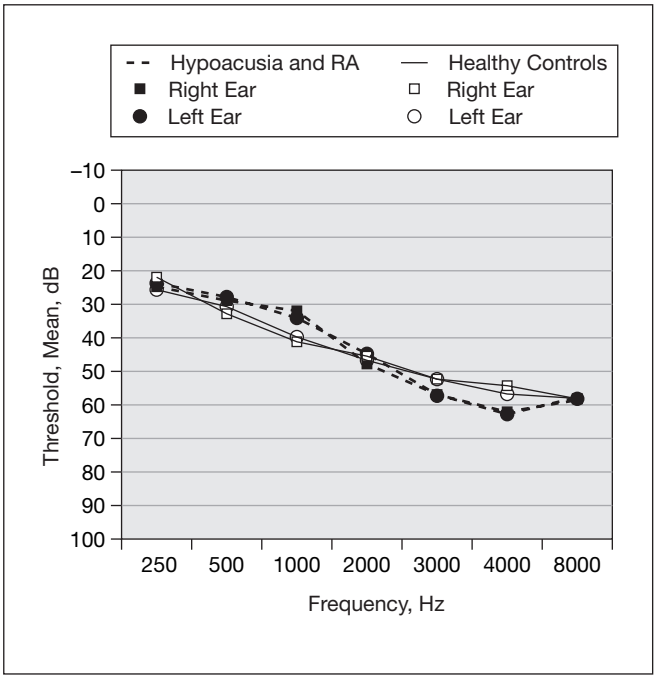

Figure 1. Mean airway thresholds obtained in the 83 subjects with hypoacusia and rheumatoid arthritis (RA) and the 17 subjects in the group of healthy controls.

Comparing the quantitative variables indicating clinical activity of RA and the percentage of binaural hearing loss detected, it was not possible to obtain straight line regression equations with a valid R coefficient. This was seen when the degree of hypoacusia was correlated with the age of the patient, the duration of the disease, the HAQ disability index, the AVS, the number of painful or swollen joints and, finally, disease activity score DAS. From the comparison of the number of parameters altered in the screening battery of each patient with RA and hypoacusia, a non-significant trend was obtained with y=0.078x+0.37 and R=0.7539, although the most marked approximation to a ratio with

Table 3. Comparative Analysis of the Cases of Rheumatoid Arthritis With or Without Hypoacusia*

	Patients With RA and Hypoacusia (n=83; 166 Ears)	*Patients With RA Without Hypoacusia (n=111; 222 Ears)*
Airway threshold at 250 Hz	24.8 (11.6) dB HL	12.4 (8.5) dB HL†
Threshold at 500 Hz	29.5 (10.9) dB HL	15.3 (6.0) dB HL†
Threshold at 1000 Hz	34.8 (11.3) dB HL	14.8 (7.1) dB HL†
Threshold at 2000 Hz	46.4 (15.7) dB HL	17.9 (6.2) dB HL†
Threshold at 3000 Hz	57.7 (12.6) dB HL	21.3 (7.3) dB HL†
Threshold at 4000 Hz	63.1 (17.3) dB HL	26.6 (7.2) dB HL†
Threshold at 8000 Hz	59.0 (17.3) dB HL	31.2 (8.9) dB HL†
Age	40.6 (9.2) years	40.4 (9.9) years
Duration of the disease	6.4 (3.4 years	7.1 (4.2) years
Patients with SB+	24 (28.9%)	22 (19.8%)†
Patients with RF+	71 (85.5%)	81 (72.9%)
Patients with WB+	10 (12.0%)	1 (0.9%)‡
GSV	33.0 (15.8) mm	26.9 (21.2) mm
HAQ Index	1.07 (0.50)	1.35 (0.72)‡
AVS Index	2.16 (1.42)	2.65 (1.62)
Swollen joints	7.9 (3.9)	6.1 (4.4)‡
Ritchie Index	3.7 (4.9)	3.2 (4.0)
Mean disease activity (DAS Index)	3.6 (2.7)	3.1 (2.8)
Patients with DAS Index >3.7	27 (32.5%)	29 (26.1%)

*Patients with recorded hypoacusia showed more alterations in the screening battery (SB) and in the Western blot (WB) test. In addition, they presented a higher number of joints involved and a higher disease activity indicator than the subjects with RA and without hypoacusia.
†P<0.001.
‡P<0.01.

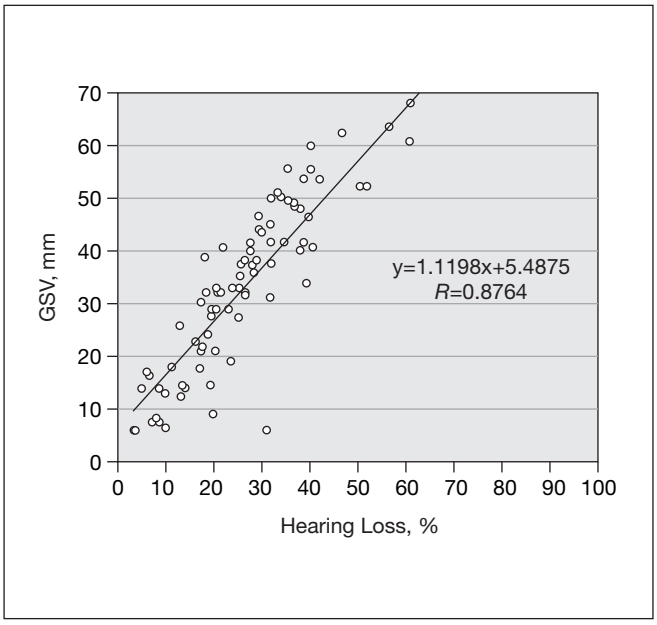

Figure 2. Straight-line regression and equation obtained from the comparison between globular sedimentation velocity (GSV) values for patients with rheumatoid arthritis and hypoacusia and the degree of binaural hearing loss recorded.

statistical significance was provided by the GSV value, represented in Figure 2

DISCUSSION

Together with systemic lupus erythematosus (SLE), RA is probably the model disease for systemic involvement in the context of an immunomediated disorder or auto-immune pathogenesis. In fact, although 5 of the 7 diagnostic criteria for this disorder refer to alterations in the joints (rigidity, polyarthritis, involvements of the hands, simultaneous symmetry, and radiological alterations), multi-organic alteration includes a potential pericardial effusion in 50% of the cases, subcutaneous nodes in 20% and pleuritis, polyneuropathy, vasculitis, amyloidotic nephropathy, and Felty's syndrome (association with neutropenia and splenomegaly).[9-11] The best-known otorhinolaryngological involvement is cricoarytenoid arthritis, more for its characteristic nature than for its frequency.[9] The sensorial alterations most commonly encountered affect sight, with frequent description of episcleritis, keratoconjunctivitis sicca, endophthalmitis and glaucoma, and they may lead to blindness.

The major treatises describing this disease do not generally mention hypoacusia in patients with RA. Nonetheless, it is an acknowledged fact that it has a higher prevalence in than in other groups of the population. To this end, the bibliography reviewed uses a diagnostic arsenal of labyrinth tests limited to the study of conversational discrimination tests, tonal threshold audiometry and tympanometry.[12-16]

The result of these revisions shows a predominance of sensorineural hypoacusia (SNH). Ozcan et al[16] observed 70.2% of individuals with hypoacusia in their group of 37 patients with RA (vs 17.1% of the controls), and specifically in 59.4% there was a significant fall in the thresholds for bone audiometry. Raut et al[13] detected up to 72.2% of patients with hypoacusia among the 35 subjects with RA (vs 39.2% of controls), with 60% of cases with SNH. In the group of Magaro, with 20 patients, the percentage of hypoacusia was 55%,[15] 36.1% in the 42 cases presented by Takatsu et al[17] and 25.2% in the 20 patients of Kakani et al.[18] Our results, with 42.7% (vs 15.9% of the controls; $P<.001$), are in the mid-point of the other groups, although they present the widest study volume of all those published. In addition, the number of patients with RA showing a threshold in excess of 30 dB HL in their airway audiometry record in more than two of the frequencies studied was 132 (68% vs 66% in the controls, without statistical significance).

The finding of a transmission component is not widespread. Our group only detected 4% of pure or mixed transmission hypoacusias (TH). Only Ozcan et al, with 24.3% of cases with mixed hypoacusia, and Raut et al, with 17.1%, found significant figures. The 2 series do not coincide in identifying the ultimate cause: hyperlassitude of the transduction mechanism or discontinuity in the ossicular chain.[13,16] Most authors do not find cases with TH and do not observe modifications in pressure in the middle ear when studying the tympanogram and stapedial reflexes.[12,14,17,19] Colletti et al,[20] using multifrequency tympanometry, do not observe any worsening of the conduction, but they do not discard the involvement of the synovial joints in the chain and attribute this conservation of hearing to a compensation of the middle ear, which raises the static pressures of the drum.

The study by Halligan et al,[21] on 29 patients in 2006, concludes with the absence of significant differences in hearing impairment with respect to a healthy control group of matched age and gender. These authors identified 59% of cases with a raised threshold in at least one frequency, versus 47% in the control group. With regard to the affected ears, these differences increased respectively to 52% and 38%. The type of hypoacusia most frequently detected in their study among subjects with RA is SNH (45%), with 14% of mixed or pure TH. However, these percentages separate somewhat when comparing modifications in the acoustic reflexes or in the conversational level, which are more strikingly marked from one case to another. Furthermore, the questionnaires on subjective hearing loss and sensation of instability are significantly more altered among these cases, a circumstance that these authors attribute more to the degree of disease activity (DAS). The record of otoacoustic emissions and tympanograms are similar in both groups. Perhaps the inclusion in this study group of patients with ages lower than those required in their inclusion criteria (not <40 years of age nor >70) might have brought the results closer in line with respect to the findings in our group, where the mean age of our 194 cases was 40.3 ± 9.6 years. It is not possible to discard a bias due to presbyacusia or comorbility among the subjects over 55 years of age and the controls in this recent complete study.

Be that as it may, the documentation of SNH in patients with RA should aim more at the possibility of its prediction, control or even its reversal, rather than the mere effort of describing it. A first step in this sense is offered by the correlation exercise carried out by some authors of the severity of hypoacusia and different clinical circumstances surrounding RA. The results so far are not hopeful. Takatsu et al[17] detected statistical significant correlations between the degree of hearing loss and the increase in GSV and the plasma concentrations of interleukin 6 and metalloproteinase 3, whereas Magaro et al[15] observe correlations when comparing hypoacusia disease activity and seropositive results for RF. Our group has not found any statistical significance resulting from the comparison of the disease with clinical characteristics of RA (number of joints affected), degree of disease activity or analytical parameters characterizing it, in line with other authors.[18,19] The high R correlation coefficients are striking, although not statistical significant, when considering the straight-line regression equations obtained in the comparison of the quantitative variables, percentage of hypoacusia with GSV values and number of tests altered in the screening battery (SB).

This SB included determinations with little sensitivity in the identification of subjects affected by immunomediation in the inner ear, but they hint at the profile of individuals with a potential active auto-immune process.[4] Auto-immune diseases are characterized by their tendency towards comorbility. In multi-organic diseases with acknowledged immunomodulated aetiopathogeny, such as RA or SLE, this association is not as frequent and the cases of RA coursing simultaneously with Sjögren's syndrome, scleroderma or thyroiditis are unusual. The auto-immune disease of the inner ear described by McCabe[22] in 1979 is no exception and its concomitance in our population is 11 cases, 12% of the patients with RA and hypoacusia versus 5.7% of the 194 subjects with RA included in the study. In fact, a positive result in the WB test predicted a functional recovery of hearing only in these cases,[4] so this might offer a physiopathological explanation.

In the rest of the patients with SNH and diagnosed as having RA, some authors offer less than enlightening rationales for cochlear dysfunction and recommend evoked potential tests or high frequency audiometry.[15,23] A few cases have been explained through an imaging study with magnetic resonance, which reveals pachymeningitis as the originating cause of the hearing impairment,[24] or by a review of the medical history when it as known that the patient had followed a potentially ototoxic anti-arthritis therapy, such as hydroxychloroquine.[25]

In any case, the general acceptance of the trend towards hypoacusia in subjects with RA makes it recommendable

to carry out a preventive audiometric study and, as far as possible, an analytical immunomediation profile including, in addition to RF and GSV, an assessment of immunoglobulins, complement and acute phase reagents, in an attempt to discriminate a potential immunomediated event in the disease. An alteration of more than three tests in the SB should lead to a more specific identification method such as WB.

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