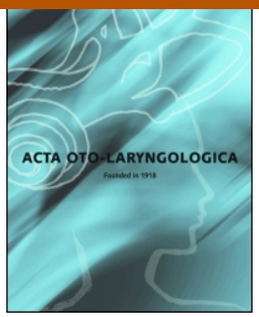

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ORIGINAL ARTICLE

Can unilateral, progressive or sudden hearing loss be immune-mediated in origin?

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ABSTRACT

Objective: The aim of the present study was to demonstrate that the positivity of nonspecific immunological tests could be found not only in bilateral hearing loss but also in unilateral cases, either sudden or progressive.

Method: An observational case series study included subjects suffering from unilateral or bilateral, sudden or progressive, symmetric or asymmetric sensorineural hearing loss (SNHL). All the patients underwent pure tone audiometry and the following battery of blood exams: anti-nuclear antibody (ANA), extractable nuclear antigen (ENA) antibody screening, anti-thyroperoxidase (anti-TPO), anti-thyroglobulin and anti-smooth muscle antibody (ASMA).

Results: The positivity to nonspecific immunological test was found in nearly 70% of the study groups. ASMA and ANA were found to be present in both bilateral and unilateral cases, without statistical difference. Considering the correlation between positivity/negativity and systemic autoimmune pathologies, in the bilateral forms of hearing loss, a high incidence of thyroid pathologies has been identified, with a higher percentage of systemic autoimmune diseases in respect to the normal population.

Conclusions: The nonspecific autoimmune tests are worth to be performed also when SNHL is not bilateral and progressive, since an immunological mechanism could also underlie unilateral and sudden SNHL cases.

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KEYWORDS
Immune-mediated hearing loss; sensorineural hearing loss; aspecific immune tests

Introduction

Since more than three decades, a bilateral, progressive form of sensorineural hearing loss (SNHL) has been regarded as a possible immune disorder that affects the inner ear. The clinical suspicion can be raised in presence of involvement of three contiguous frequencies [1], rapid progression over days to months [2] and a positive response to corticosteroids treatment [3]. Hence, the term of autoimmune or, better, immune-mediated inner ear disease (IMIED) has been coined. This nosological entity is thought to be caused by antibodies or immune cells that attack the inner ear and it may present as a localized primary disease or in association with a systemic autoimmune disorder [3,4].

Elevated levels of sera immune complexes and anti-inner ear antibodies have been described on patients affected by progressive and/or sudden SNHL [5]. The reaction of sera of patients with suspected IMIED showed a positive reaction of their sera – at 68 KDa antibody – with HSP-70 proteins extracted from bovine inner ear as well as with the human 'choline transporter-like protein 2' or CTL2 [6,7]. In this regard, some authors have proposed a higher sensitivity of nonspecific immunological tests for the detection of IMIED [8]. Nevertheless, there is no consensus about the type of diagnostic laboratory test that could correctly identify an IMIED, due to their low grade of sensitivity and specificity [6,9]. As far as nonspecific antigen-screening tests are concerned, some studies would suggest restricting the laboratory tests only to anti-nuclear antibodies (ANA), to immune-phenotype of peripheral blood lymphocytes (PBL) [8] and to anti-endothelial antibodies (AECA) [10].

From an audiological point of view, it is common belief that immune-mediated hearing loss generally involves both ears (80%), with symmetric or asymmetric hearing threshold levels [4,11,12], although at its initial presentation, IMIED may present in a fashion similar to that seen in sudden SNHL, and involves only one ear [10,11].

The aim of the present study was to investigate on the diagnostic role played by some nonspecific immunological tests for substantiating the diagnosis of IMIED, and to test them on a cohort of patients that also includes the unilateral and sudden forms of SNHL, other than the classical bilateral and progressive forms.

Material and methods

A consecutive series of subjects affected by unilateral or bilateral, sudden or progressive, symmetric or asymmetric SNHL were included in this study. Patients with diagnosis of definite Menière's disease, retrocochlear pathologies or over 65 years were excluded.

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All the patients underwent pure tone audiometry and the following battery of blood exams to evaluate the immunological response:

- anti-nuclear antibody (ANA),
- extractable nuclear antigen (ENA) antibody screening,
- anti-thyroperoxidase (anti-TPO),
- anti-thyroglobulin
- anti-smooth muscle antibody (ASMA).

ANA determination was performed by indirect immunofluorescence (IIF) and the definition of positivity expressed as titre of 1:80, considering the values $>80<120$ as slightly positive, >120/160 mildly positive and >160 highly positive. ENA screening was performed with the immuno-enzymatic assay ELISA: the reference titre was <20 and the positivity was considered slight for 20, mild for >20, high for ≥40. The determination of ASMA autoantibody was performed by IIF, having as reference titre the dilution of 1:40, considering slight positivity 1:40, mild 1:80 and high 1:100. Sera positivity for anti-thyroglobulin and anti-thyroperoxidase (anti-TPO) autoantibody, identified by immunochemiluminescence, were titred >40 UI and >35 UI, respectively.

According to the hearing threshold at the time of observation, the patients were divided into two groups:

- Group A, which included 39 patients affected by bilateral hearing loss (BHL);
- Group B, with 33 patients affected by unilateral hearing loss (UHL).

The BHL group was further divided into symmetric (BHLsy, $n=29$ patients, 74.35% of the total) and asymmetric (BHLasy, $n=10$ patients, 25.65% of the total). The UHL group was further divided into sudden (UHLs, n.22, 66.67% of the total) and progressive (UHLp, n.11) (33.33% of the total).

The incidence of the positivity to nonspecific antibodies was evaluated in the whole study sample and in the individual subgroups, and their correlation has been statistically evaluated. The correlation between the positivity for the individual antibody and the coexistence with systemic autoimmune diseases has also been investigated. A positivity scale was arbitrarily assigned to the assessed autoantibodies, with a score between 1 and 3, where 1 represents slight positivity, 2 mild positivity and 3 high positivity. A statistical two pair sample test (t-test) was applied for the evaluation of the difference of positivity scores between Groups A and B. The results were compared with a control group (C), composed of 35 outpatients admitted for pathologies that were not involving hearing.

The incidence of coexistence of a systemic autoimmune disease was evaluated in both groups and the correlation between systemic autoimmune disease and nonspecific autoantibody positivity and negativity was also analysed.

The study was conducted in accordance with the Ethical Standards of the Local Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Results

Seventy-two patients (24 males and 48 females, with a mean age of 46.8 years, min. 14, max. 72) came to our observation with an IMIED suspicion.

The nonspecific immunological tests resulted positive in 48 patients (66.67%) of the entire study group. In the BHL group, positivity was found in 26 patients (66.7%): 80.8% of them were affected by symmetric SNHL and 19.2% by asymmetric SHNL. A negative test was found in 33.3% of the BHL patients, 61.5% affected by symmetric SNHL and 38.5% by asymmetric SNHL (Figure 1). In the BHLsy group, 72.4% of patients resulted positive and 27.6% were negative. In BHLasy group, 50% resulted positive and 50% negative (Figure 2). In the UHL group, positivity was found in 66.7% of the patients (Figure 1). Among the 22 patients affected by sudden SNHL, 59.1% resulted positive and 40.9% negative; among the 11 patients with progressive SNHL, 81.8% resulted positive and 18.2% negative (Figure 3).

Considering altogether the bilateral and unilateral progressive SNHL ($39+11$ patients), a 70% of positivity to nonspecific immunological tests was found.

As far as the positivity for the individual immunological test is concerned, ANA resulted positive in 30.7% of BHL and 33.3% of UHL; ENA resulted positive in 12.8% of BHL and 3% of UHL, ASMA resulted positive in 23.1% of BHL and 27.3% of UHL; anti-thyroglobulin antibodies resulted positive in 10.2% of BHL and 24.2% of UHL; and anti-thyroid peroxidase (anti-TPO) antibodies resulted positive in 18% of BHL and 24.2% of UHL (Figure 4). No statistical difference in scores of positivity scale between bilateral and unilateral forms was found. In the control group (C), ANA was found positive in 17.14% [6] of the patients, with a low titre (1:40), while ASMA resulted negative in the whole control group.

Regarding the ANA and ASMA titres, no statistically significant difference was found between BHL and UHL groups, for both parametric and non-parametric tests (Table 1).

Among the BHL patients who resulted positive to nonspecific autoantibody ($n=26$), 3 (11.5%) had a systemic autoimmune disease associated to thyroid disease, 7 (26.9%) had only a systemic autoimmune disease and 3 (11.5%) had an isolated thyroid disease. In the patients of the same group, in whom the nonspecific auto-antibodies tests were negative ($n=13$), none had systemic autoimmune disease associated to thyroid disease, 2 (15.4%) had only a systemic autoimmune disease and none had only a thyroid disease.

Among UHL patients who showed positivity for nonspecific autoantibody ($n=22$), 1 (4.5%) had systemic autoimmune disease associated to thyroid disease, 2 (9%) had only systemic autoimmune disease and 7 (31.8%) had only thyroid disease. In those patients of the same group who were negative to nonspecific autoantibody ($n=11$), 1 (9%) had only systemic autoimmune disease and none showed a

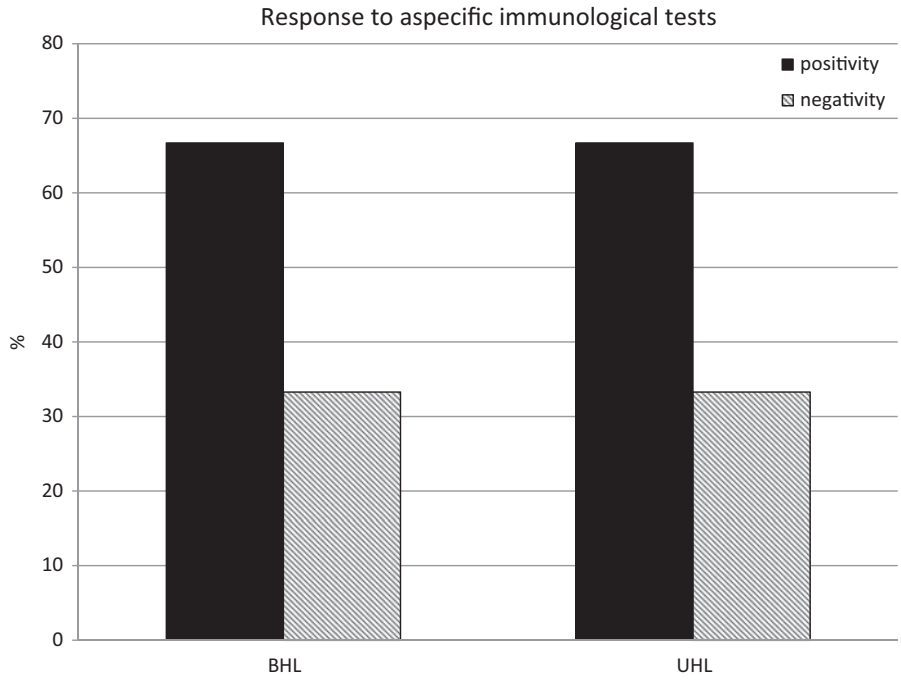

Figure 1. Percentage of nonspecific immunological tests positivity and negativity in the study groups. BHL: bilateral hearing loss; UHL: unilateral hearing loss.

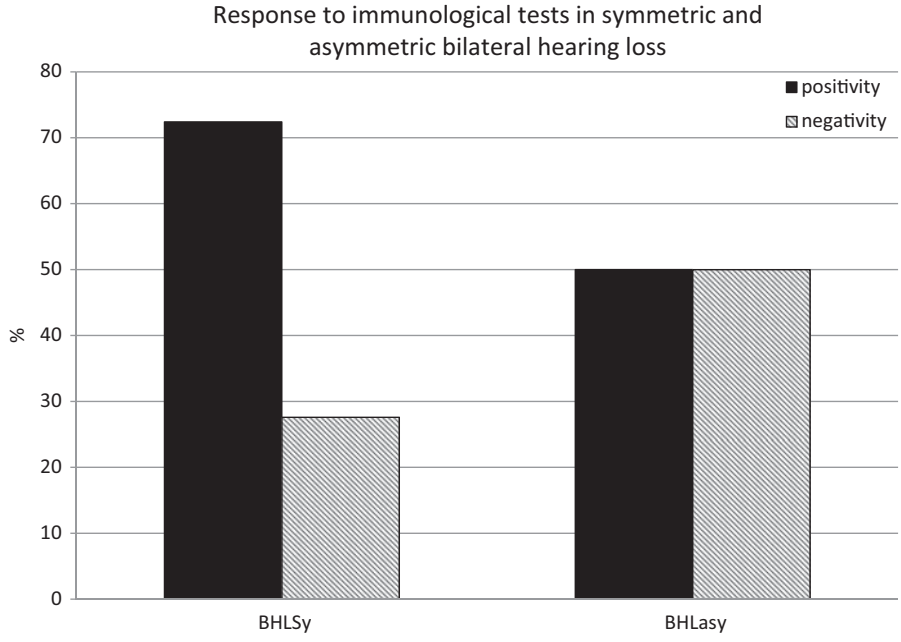

Figure 2. Percentage of positivity to nonspecific immunological tests in symmetric and asymmetric bilateral hearing loss. BHLsy: symmetric bilateral hearing loss; BHLasy: asymmetric bilateral hearing loss.

systemic autoimmune disease associated to thyroid disease or thyroid disease only (Figure 5).

Discussion

The typical profile of a suspected IMIED is actually based on specific features that include the clinical course, the immunological changes and the positive response to the steroid therapy [12]. The pivotal element is represented by the presence of hearing loss that usually drives the clinician to further investigations, also on the ground of specific characteristics, that is, if being uni- or bilateral and sudden or progressive. When initially described, in fact, the IMIED was recognised as always being both bilateral and progressive, if not rapidly progressive [13]. When considering the immunological component of this inner ear disorder, one may recall that some evidence has been collected for the inner ear to be affected in a variety of non-organ-specific autoimmune diseases as a result of the interaction of genetic factors, environmental pathogens and immune system responses [14]. An autoimmune activity in idiopathic hearing loss has been documented in viral labyrinthine infections

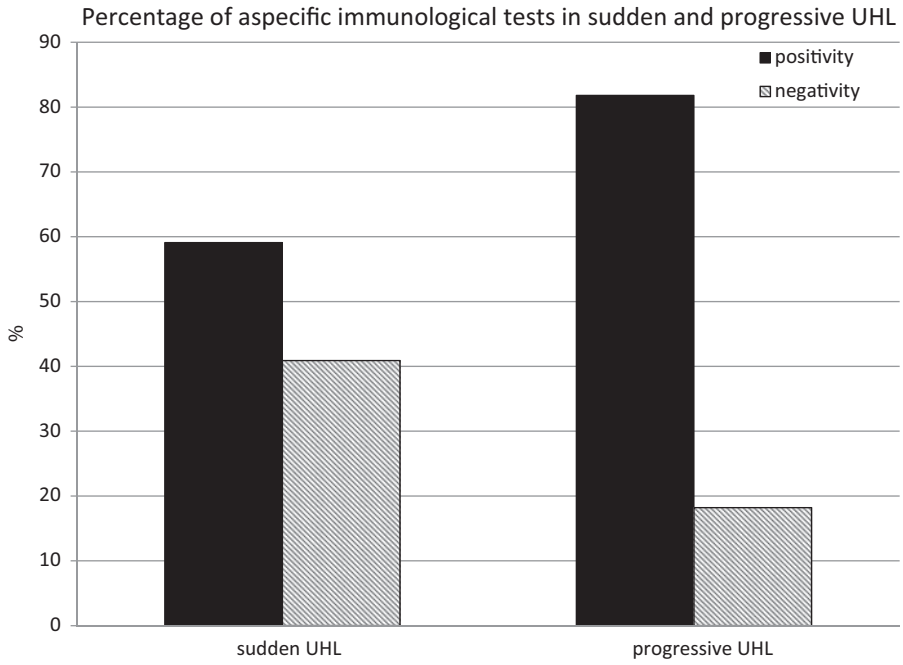

Figure 3. Percentage of nonspecific immunological tests in sudden and progressive unilateral hearing loss. UHL: unilateral hearing loss.

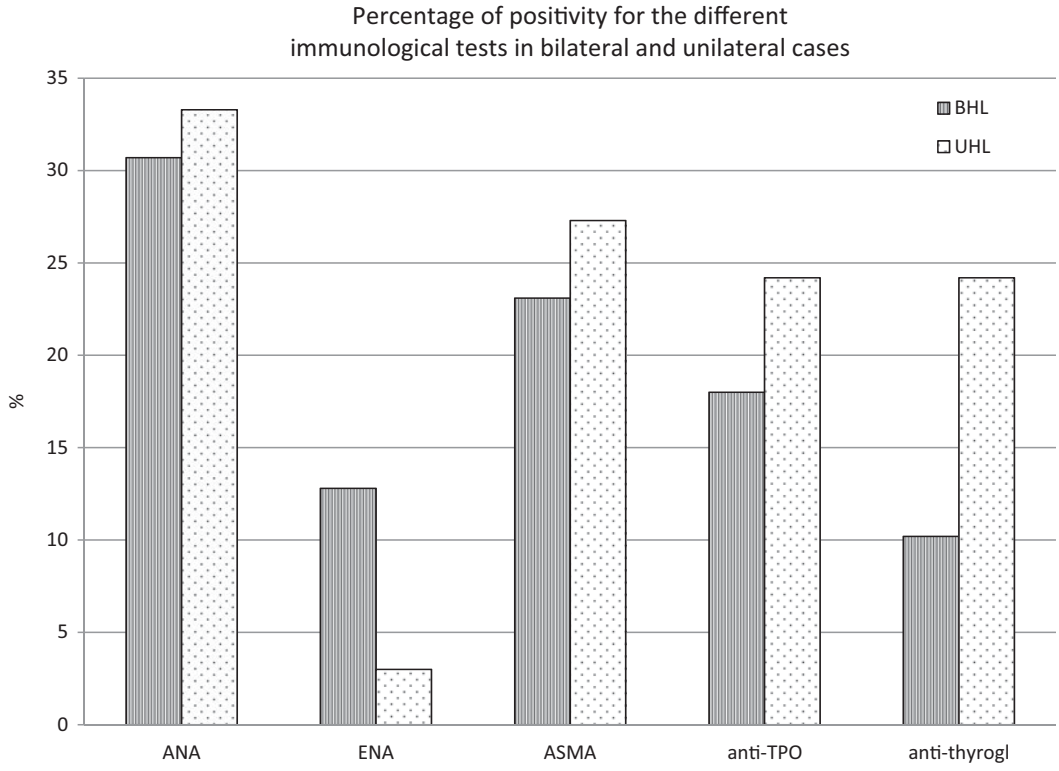

Figure 4. Percentage of positivity for each nonspecific immunological test in bilateral hearing loss (BHL) and unilateral hearing loss (UHL). ANA: anti-nuclear antibody; ENA: extractable nuclear antigen antibodies; ASMA: anti-smooth muscle antibody; Anti-TPO: anti-thyroperoxidase; Antithyrogl: anti-thyroglobulin.

considered as the major causes of auditory and vestibular system pathologies, where the viral and bacterial infections may contribute to the development and exacerbation of autoimmune diseases [4,15,16]. The inner ear appears to be the target for an immune-mediated disease that can be organ or non-organ specific and the disease seems to have some analogy with rapidly progressive glomerulonephritis: if not treated, also often more quickly than 3 months, the pathology may progress to a severe and irreversible damage [15]. More specifically, ultrastructural signs of degeneration of the inner ear structures, with atrophic changes of the acoustic nerve and development of endolymphatic hydrops have also been described [17]. As aforementioned, the clinical profile might rise the suspicion of an IMIED, when major and/or minor criteria are taken into consideration: BHL, systemic autoimmune diseases, ANA >1:80, decrease of native T cells and

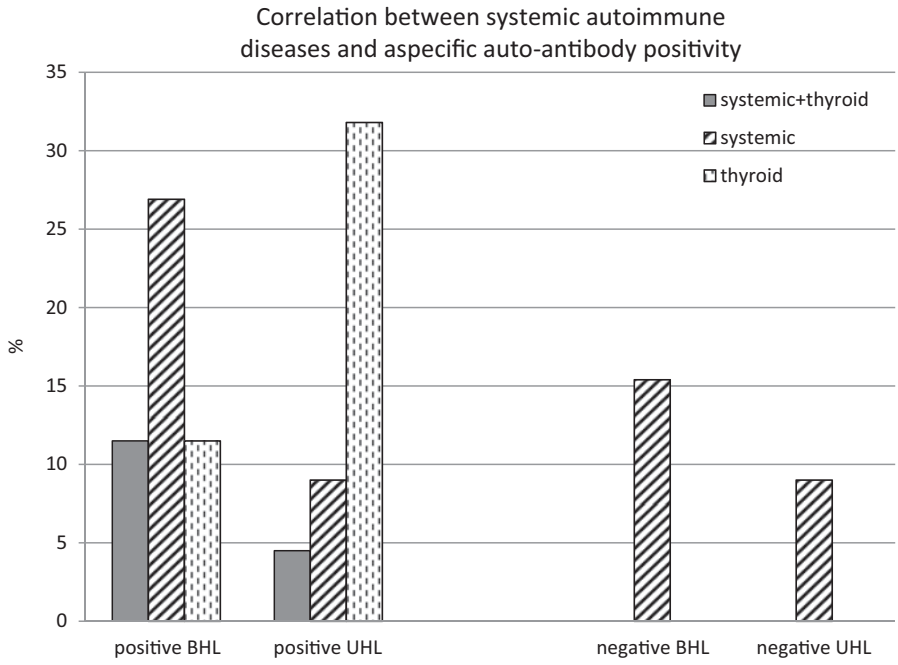

Figure 5. Correlation between systemic autoimmune diseases and nonspecific autoantibody positivity and negativity in bilateral hearing loss (BHL) and unilateral (UHL) hearing loss.

hearing recovery rate for corticosteroid >80% represent the major ones; while unilateral hearing loss, young or middle age of the patient, the female gender and hearing recovery rate <80% for steroids play a minor role [18].

The purpose of the present study has been the assessment of an IMIED as it can be solely based on the audiological and nonspecific laboratory data, while the other important feature for the diagnosis, that is, responsiveness to steroids as *ex juvantibus* factor, was not at all taken into consideration. Among the possible audiological pictures, also the presence of an atypical presentation, such as it could be considered a unilateral or a sudden form of hearing loss, has therefore purposely included, so as to compare two groups of subjects with SNHL and their eventual positivity to nonspecific blood tests, chosen among those more frequently positive in systemic autoimmune diseases (ANA, ENA, ASMA anti-TPO and anti-thyroglobulin).

In this regard, despite its introduction and wide use during the '90s, the Western Blot determination of HSP-70 (OTOblot) has lost much of its diagnostic importance for IMIED, showing to be less sensitive than the ANA test, due to the high percentage of positive values in the normal population [8]. In this regard, a personal investigation carried out on 56 patients, presenting with both unilateral and bilateral SNHL (unpublished data) showed that none of the patients with unilateral SNHL was OTOblot positive, against the 58% positivity of nonspecific immunological tests; and only 9% of bilateral SNHL were OTOblot positive against the 59% positivity of the nonspecific immunological tests. In addition, all the OTOblot positive patients displayed positivity to the nonspecific immunological tests. These findings altogether have motivated the discontinuation, in our clinical practice, of routine OTOblot and, instead, the use of nonspecific laboratory tests that were the object of the present study.

Table 1. ANA and ASMA positivity scores in bilateral hearing loss (BHL) and unilateral hearing loss (UHL): no statistically significant differences were found between the two groups (>0.05).

ANA		ASMA	
Bilateral HL	Unilateral HL	Bilateral HL	Unilateral HL
2	1	1	1
1	1	1	1
3	1	1	3
1	1	1	2
1	1	2	1
2	1	2	1
3	1	1	1
1	1	1	1
1	2	1	2
1	2		
1	3		
3	1		

ANA: anti-nuclear antibodies; ASMA: anti-smooth muscle antibodies.

When considering the ANA test, it should be kept in mind that its positivity in the normal population increases with age so that, in order to be significant, its titre values need to be particularly high, that is, >1:160, as it was taken as a reference also in the present study [7,10,14]. Our findings have, in fact, confirmed the relevant positivity of ANA test, both in progressive and bilateral forms, but without significant differences between the two study groups.

According to the literature data and to our findings, the ENA screening test would play as second line diagnostic investigation, whilst the other antibodies (ASMA, anti-thyroglobulin and anti-TPO), whose positivity was assessed in some inner ear pathologies, such as Menière's disease, did not show in our experience a similar sensitivity for IMIED. Apart from the class of the selected antibodies, our study would also suggest the importance of considering the appropriate titre values, considering that they could be higher in the elderly general population.

Our results have also shown that the positivity for nonspecific tests plus the organ-specific anti-thyroid test was high (66.7%) in both groups (unilateral and bilateral), without statistically significant differences. A high positivity was found for ANA and ASMA, but both in bilateral and unilateral cases and without differences in the scale of positivity, whilst a statistical significant difference was found in comparison to the normal population.

Moreover, when evaluating the coexistence of a systemic autoimmune disease or a thyroid disease and their associations, both bilateral and unilateral SNHL showed a significant correlation only with an active thyroid disease. As far as the correlation between the thyroidal pathology and the positivity for anti-thyroglobulin and anti-TPO in the two main study groups is concerned, a high correlation was found in both groups, with higher values in the unilateral group. It is therefore our opinion that it would be useful to add to ANA and ASMA tests also the titration of anti-thyroglobulin and anti-TPO antibodies, especially in patients suffering by unilateral SNHL without evidence of thyroid pathology.

In bilateral SNHL subjects, a higher percentage of positivity was found in the symmetric forms that, therefore, would seem to be highly correlated to the nonspecific positivity to autoantibody test.

Another interesting finding from our study is that the positivity of the nonspecific battery test was higher in the sudden SNHL group. One may thus suggest that the unilateral SNHL, when sudden in onset, is more likely to have a contralateral involvement over time than the unilateral, progressive form.

On the base of this experience, it is likely to assume that the nonspecific antigen screening tests retain a higher diagnostic value in respect to the specific ones. The diagnostic value of nonspecific autoantibody is not dependant from a cause–effect relation, but is rather related to an epidemiological and statistical association, so that the positivity to a particular autoantibody might provide important information regarding the disease profile, the responsiveness of patients to the therapy and could also eventually differentiate the prognosis.

A systemic disease should produce bilateral rather than unilateral ear symptoms. As a consequence of an immunological mechanism in the pathogenesis of SNHL, it could also be supposed that both sides could be compromised. The present study has shown that the detection of serological nonspecific inner ear auto-antibodies, such as ANA and ASMA, that are highly positive in the suspected IMIED in respect to the general population, may be useful to suggest a non-organ-specific immune mediated disorder, not only in bilateral SNHL but also in the unilateral forms. The detection of anti-thyroglobulin and anti-TPO may be useful in suspected IMIED not only in patients with systemic autoimmune diseases but mostly in those who are asymptomatic for this kind of pathologies. Further studies on a larger population sample would be necessary to support this hypothesis and to clarify the eventual simultaneous modification of hearing loss and autoantibody levels with time and therapy.

Disclosure statement

No financial support for the work and other financial or personal connections to the work need to be declared.

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