Clinical and Experimental Rheumatology 2024; 42: 2268-2271

Autoimmune inner ear disease associated with antiphospholipid antibodies

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Received on February 26, 2024; accepted in revised form on May 20, 2024.

Key words: neurosensorial hearing loss, autoimmune inner ear disease, antiphospholipid antibodies

Competing interests: none declared.

ABSTRACT

Objective. *The percentage of autoimmune diseases in Western countries is approximately 8% of the total population. Despite numerous studies indicating an increase in prevalence and incidence over the past two decades, autoimmune vestibular disorders seem to be underdiagnosed, primarily due to the lack of a definitive test capable of identifying the specific antigen of the inner ear. Autoimmune inner ear disease (AIED) is defined as a rapidly progressive and often fluctuating bilateral neurosensorial hearing loss that develops over a period of weeks or months. AIED can affect only the inner ear or be part of systemic diseases such as granulomatosis with polyangiitis, Cogan's syndrome, systemic lupus erythematosus, polyarteritis nodosa, or relapsing polychondritis, among others. Our main objective was to conduct a study on the presence of antiphospholipid antibodies (aPL) in patients with AIED seen in a specialised clinic.*

Methods. *We designed an observational retrospective study in which we selected patients from a total group of 55 with AIED referred to the Autoimmune Diseases Clinic, those with confirmed positivity for antiphospholipid antibodies, and described their clinical, analytical, and epidemiological characteristics.*

Results. *We found a prevalence of 29% positivity for antiphospholipid antibodies, with lupus anticoagulant (LA) being the most frequently detected, followed by anticardiolipin (aCL) and anti-beta2 glycoprotein (anti-B2GP). Double positivity was observed in 25% of patients. The main clinical manifestations were bilateral hearing loss, vestibular symptoms, and tinnitus. Only 25% of patients experienced audiometric improvement during the course of the disease.*

Conclusion. *We emphasise the importance of identifying the presence of aPL in AIED, enabling the establishment of appropriate and specific therapeutic management to prevent audiometric deterioration.*

Introduction

Autoimmune inner ear disease (AIED) was first described in 1979 (1). It is part of the broad group of neurosensorial hearing losses, representing less than 1% of cases, with an incidence of around 5 cases per 100,000 people per year (2). The prevalence is higher in women and in the age group between 20 and 50 years. It can be associated with a systemic autoimmune disease in 15 to 30% of cases (3). In 80% of cases, it presents bilaterally, although involvement of the opposite ear may occur after months or years. Neurosensorial hearing loss must be at least 30 dB, with evidence of progression in at least one ear in two successive audiograms performed over 3 months (4). The diagnosis of AIED remains a challenge since there are no reliable specific tests. It is fundamentally based on clinical evaluation and should always be suspected in a patient with rapidly progressive idiopathic neurosensorial hearing loss. García-Berrocal *et al.* proposed diagnostic criteria, requiring the fulfilment of at least 3 major criteria or 2 major and 2 minor criteria to confirm the diagnosis (5):

- Major criteria: bilateral hearing loss, systemic autoimmune disease, ANA titre >1:80, reduction of T lymphocytes (CD4), and auditory recovery rate after corticosteroid therapy >80%.
- Minor criteria: unilateral hearing loss, young or middle-aged patients, female sex, and auditory recovery rate after corticosteroid therapy <80%.

Among the analytical tests, the utility of including the erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), and rheumatoid factor (RF) in the assessment of these patients has been established. However, the detection of anticochlear antibodies (ACLA) is highly controversial (6-7). They are usually used empirically in clinical practice, and their role in pathogenesis and diagnostic utility has not been established (8). Some authors have shown that ACLA is expressed without significant difference in patients with immunomediated disease with and without neurosensorial hearing loss (9). Antiphospholipid antibodies (aPL) are a heterogeneous family of immunoglobulins that recognise different protein components or factors (*e.g.*

Table I. The main characteristics of the16 patients included in the study.

Case	Age (years)	Sex	History of thrombosis	Clinic	Cardiovascular risk factors	Antibodies	Antiphospholipid syndrome	Treatment
1	35	Male	No	Bilateral hearing loss, headache, vestibular, tinnitus	No	Confirmed positive LA	No	Corticosteroids
2	57	Female	No	bilateral hearing loss, headache, vestibular, tinnitus	AH	Confirmed positive LA	No	ASA
3	60	Male	DVT	bilateral hearing loss, vestibular, tinnitus	Dyslipidaemia, Smoking	Confirmed positive LA	Primary	ASA, anticoagulation
4	55	Female	No	Unilateral hearing loss, vestibular, tinnitus	No	LA and Anti-B2GP positive confirmed	No	Corticosteroids, ASA, other Immunosuppressant
5	65	Female	No	bilateral hearing loss, vestibular	AH	LA, anticardiolipin and Anti-B2GP positive confirmed	No	Corticosteroids, ASA
6	33	Female	No	Bilateral hearing loss, vestibular, tinnitus	No	Confirmed positive LA	No	Corticosteroids, other Immunosuppressant
7	61	Male	No	Bilateral hearing loss, vestibular	AH, Smoking	Confirmed positive LA	Primary	Corticosteroids
8	34	Female	No	Bilateral hearing loss, vestibular	No	Confirmed positive LA	No	No
9	51	Female	Abortion, DVT	Unilateral hearing loss, headache	No	Confirmed positive anticardiolipin and anti-B2GP	Secondary (SLE)	Corticosteroids, ASA, other immunosuppressant
10	70	Male	No	Bilateral hearing loss, vestibular	Dyslipidaemia, Smoking	Confirmed positive LA	No	No
11	64	Male	DVT	Bilateral hearing loss, vestibular	Dyslipidaemia, Smoking	Confirmed positive LA	Secondary (PAN)	Corticosteroids, anticoagulation
12	69	Female	No	Bilateral hearing loss, vestibular, tinnitus	Dyslipidaemia	Confirmed positive LA	No	ASA
13	52	Female	No	Bilateral hearing loss	AH, Smoking	Confirmed positive anticardiolipin and anti-B2GP	No	ASA
14	59	Male	DVT	Bilateral hearing loss, tinnitus	No	LA, anticardiolipin and Anti-B2GP positive confirmed	Primary	Corticosteroids, anticoagulation
15	59	Female	DVT	Bilateral hearing loss, headache, vestibular, tinnitus	No	LA and positive anticardiolipin confirmed	Primary	Corticosteroids, anticoagulation, other immunosuppressant
16	48	Female	DVT	Bilateral hearing loss, headache, vestibular, tinnitus	AH, Smoking	Confirmed positive anticardiolipin	Primary	Corticosteroids, ASA

annexin V, prothrombin, protein C and protein S) with an effect on the procoagulant and anticoagulant mechanisms that take place in the membranes of some cells, being part of the laboratory criteria for the diagnosis of aPL. While the most frequent manifestations in antiphospholipid syndrome (APS) are arterial and venous thrombotic events as well as obstetric complications, among the non-criteria clinical manifestations, in a recent study neurological involvement was the third most frequent (18%) (10), although there are no specific data on inner ear involvement.

However, there is a growing number of reports suggesting an association between the presence of aPL and audiovestibular dysfunction, probably due to secondary damage from microthrombosis involvement of the cochlear vessels.

Materials and methods

A descriptive cross-sectional study was conducted using patients meeting AIED criteria referred to the Autoimmune Diseases Clinic at Virgen de las Nieves University Hospital in Granada from January 1, 2021, to December 31, 2023. From an initial sample of 55 patients, an initial determination of aPL was made for all, followed by a second determination after 12 weeks for confirmation. All cases meeting AIED criteria and confirmed positivity for at least one antiphospholipid antibody were included: lupus anticoagulant [detected according to the guidelines of the International Society on Thrombosis and Haemostasis (11)]; IgG, IgM, or both anticardiolipin antibodies (serum or plasma with medium to high titre measured by enzyme-linked immunosorbent assay-ELISA), and IgG, IgM, or both anti-β2-glycoprotein-1 antibodies (titre above the 99th percentile by ELISA). Patients with unconfirmed positivity for aPL or previously known autoimmune disease were excluded. After applying inclusion and exclusion criteria, 16 patients were included. Demographic variables (age, sex, presence of cardiovascular risk factors),

clinical variables (history of thrombosis, associated symptoms, presence of APS criteria, treatment, and audiometric evolution), and analytical variables (presence of antinuclear antibodies, type of antiphospholipid antibody, thrombocytopenia) were analysed. The revised 2006 criteria were used for the diagnosis of APS.

Results

Out of the 55 patients with AIED attended in the clinic, 16 were included for meeting the inclusion criteria (29%). The mean age of the patients was 54.5 (SD 11) years, with 37.5% being males and 62.5% females. Table I summarises the main characteristics of the 16 included patients. 56.25% of patients had cardiovascular risk factors: arterial hypertension (5/16; 31.25%), smoking (6/16; 37.5%), dyslipidaemia (4/16; 25%). In 37.5%, there was a combination of two of them. 6 of them (37.5%) had a history of thrombosis, and 1 of them (6.25%) had a history of abortion. Regarding clinical manifestations, hearing loss was predominantly bilateral (14/16; 87.5%), with vestibular manifestations (dizziness, sensation of instability, vertigo) (13/16; 81.25%), tinnitus (9/16; 56.25%), and headache (5/16; 31.25%) being frequent. Analytically, the most frequently detected antibody was lupus anticoagulant (LA) (13/16; 81.25%), followed by anticardiolipin (aCL) (6/16; 37.5%) and anti-beta2 glycoprotein (anti-B2GP) (5/16; 31.25%). It is noteworthy that double positivity was present in 25% (4/16) of cases, and triple positivity in 12.5% (2/16). Antinuclear antibodies were positive in 56.25% (9/16) of patients, and thrombocytopenia (platelets <150,000/mm^3) was detected in only one patient (6.25%). 7 out of 16 cases (43.75%) met the classification criteria for APS, mostly primary (5/7; 71.4%). The treatment used primarily consisted of corticosteroids (9/16; 56.25%), aspirin at antiplatelet doses (8/16; 50%), anticoagulation (4/16; 25%), or a combination of them (9/16; 56.25%). The auditory evolution in the majority of cases was towards worsening audiometry (9/16; 56.25%), with improvement observed in only 25% (4/16) of control audiograms.

Discussion

Although the relationship between AIED and the presence of aPL is known, there are currently only case reports of patients with APS (12-16). The characteristic triad of APS includes the presence of specific antibodies, arterial or venous thrombosis, and/or complications during pregnancy. This syndrome is associated with microthrombosis, leading to cutaneous manifestations such as purpuric eruptions, livedo reticularis and cutaneous ulcerations. Involvement of the inner ear has been reported in relation to APS and may be linked to antibodies directed against the small vessels of the labyrinthine circulation. It is suggested that endothelial cells of the cochlear circulation could be directly activated by aPL or induce the formation of free radicals, causing secondary damage to the endothelium. These positively activated endothelial cells could initiate the formation of local microthrombi and subsequent ischemia in the target organ (15). Naarendorp and Spiera (12) were the first to report the association between aCL or LA antibodies and sudden neurosensory hearing loss in six patients with systemic lupus erythematosus. Toubi *et al*. (14) studied sudden and progressive neurosensory hearing loss in 30 patients, demonstrating that in the control group, no one had aCL antibodies, while 27% of the patient group had aCL antibodies in low to moderate concentrations. In subsequent studies, Toubi *et al*. (15) reported that 31% of patients with idiopathic neurosensory hearing loss were positive for aCL, compared to only 6% of matched control subjects. In a prospective study (16) with 168 patients with progressive neurosensory hearing loss, blood analysis was performed to detect autoimmune diseases, including aCL antibodies, anti-B2 glycoprotein, and LAC. In this population, forty-two patients (25%) had at least one elevated antiphospholipid antibody marker, and twenty patients had two or more positive results in the tests, suggesting the possible involvement of aPL in the pathogenesis of some forms of inner ear dysfunction related to the formation of microthrombi in the labyrinthine vasculature. These results are similar to those found in our series, where we observed a prevalence of 29% positivity for at least one antiphospholipid antibody in patients with neurosensory hearing loss. The treatment of audiovestibular symptoms should be aimed first at preserving function, such as preserving and/or restoring hearing in patients with neurosensory hearing loss, and then addressing disability, discomfort, and quality of life. The most common treatment for AIED involves the systemic or intratympanic administration of high doses of corticosteroids, along with other immunosuppressants. However, in patients with APS, chronic treatment with low doses of aspirin may improve auditory impairment (17). The use of hearing aids is reserved to support residual hearing function or cochlear implants in cases of severe and profound neurosensory hearing loss.

Conclusions

This study supports previous research on the role of aPL in the pathophysiology of immune-mediated neurosensory hearing loss, describing a prevalence of aPL positivity of 29%. The most frequently identified antibody is lupus anticoagulant, with double positivity observed in 25% of cases. It is crucial to determine whether there is a primary or secondary APS for therapeutic management (43.75% in our series). The overall prognosis indicates worsening audiometry in more than half of the cases, although improvement is noted in 25%.

With this work, we emphasise the importance of determining aPL in patients with neurosensory hearing loss and AIED, actively seeking the presence of a possible APS, and establishing appropriate and targeted therapeutic management to prevent audiometric deterioration.

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