


Autoimmune inner ear disease (AIED): A diagnostic challenge

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Abstract

Autoimmune inner ear disease (AIED) has been defined as a condition of bilateral sensorineural hearing loss (SNHL), caused by an ‘uncontrolled’ immune system response. The inner ear can be the direct target of the immune response, but it can be additionally damaged by a deposition of circulating immune complexes or by systemic immune-mediated diseases. The clinical expression of immune-mediated inner ear disease shows a progressive bilateral and asymmetric SNHL profile, which typically benefits from a steroid and immunosuppressive therapy. The onset of AIED is between 3 and 90 days. Cochlear symptoms can be associated with vestibular disorders and in 15%–30% of cases, AIED occurs in the context of a systemic autoimmune disease. Currently, the onset of immune-mediated SNHL is not a well-understood process and the pathogenetic mechanisms of AIED remain unclear. Furthermore, there are no standardized diagnostic criteria or reliable diagnostic tests for the diagnosis of AIED. Hence, the definition of immune-mediated cochleovestibular disorders is a challenging diagnosis based on exclusion. A close collaboration between otolaryngologists, audiologists and rheumatologists is recommended, in order to achieve the multidisciplinary management of this rare entity, since an early AIED identification and a prompt medical treatment might result in acceptable hearing outcomes. The paper describes the clinical features of AIED and offers a diagnostic flow-chart to use in the clinical assessment of this condition.

Keywords

AIED, autoimmune disease, hearing loss, immune system, inner ear, steroids

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Introduction

The autoimmune inner ear disease (AIED) has been defined as a condition of a bilateral sensorineural hearing loss (SNHL), caused by an ‘uncontrolled’ immune system response. The estimated yearly incidence of AIED is <5 cases per 100,000 and its estimated prevalence is about 15/100,000 (in the United States, the expected annual AIED prevalence is 45,000 patients); it is reported that AIED is more prevalent in women, in their third and the sixth decades of life.^{1–3} AIED is considered to be responsible for <1% of all SNHL cases, even if many AIED cases might remain un-diagnosed due to the fact that specific diagnostic tests are not

currently available.⁴ The clinical expression of AIED is a progressive bilateral and not always symmetric SNHL, progressively developing between 3 and 90 days,⁵ which typically benefits from a steroid and immunosuppressive therapy. AIED is considered ‘primary’ when the inner ear is the only

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Table 1. Literature evaluation and selection, according to PRISMA criteria (<http://www.prisma-statement.org/>).

Total number of articles obtained by PubMed, Embase and Cinahl search	385
Other papers from references in the published literature	64
Total number of papers identified	449
Paper excluded ^a	265
Article assessed for eligibility	184
Paper excluded ^b	134
Total number of papers finally identified	50

^aInclusion criteria were clinical series, review papers. Exclusion criteria were not availability of a full text; manuscripts not in the English language; case reports.

^bInclusion criteria were for clinical series, papers with an adequate group of patients studied ($n > 20$); for reviews, papers published on relevant journals and papers showing a rigorous method and rigorous reporting.

organ affected; however, in 15%–30% of cases, AIED is ‘secondary’, as it occurs in the contest of a systemic autoimmune disease.^{2,4} The objective of the paper is (1) to describe the clinical features and (2) to present a diagnostic flow-chart for the diagnostic assessment of AIED.

Methods

The PubMed, Embase and Cinahl databases were searched for the last 10 years (from January 2008 up to December 2017). Full-text articles were obtained in cases where the title, abstract or key words suggested that the study might be eligible for this review. The searched medical subject heading (MeSH) terms included the following search keys: autoimmune disease, hearing loss, immune system, inner ear.

The search was conducted according to Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA) criteria/guidelines (<http://www.prisma-statement.org/>): it was carried out independently and was restricted to papers in the English language (see Table 1). Inclusion criteria were clinical series and review papers. Exclusion criteria were (1) not availability of a full text; (2) manuscripts not in the English language and (3) case reports.

Initially, the total number of papers identified was 385, but other papers (64) were also identified from references in the published literature for a total of 449 documents. The authors critically evaluated the selected papers, by reading abstracts and/or texts, to decide whether the identified papers

were relevant to this search or not. In this case, inclusion criteria were for clinical series, papers with an adequate group of patients studied ($n > 20$); for reviews, papers published on relevant journals and papers showing rigorous methods and rigorous reporting. Finally, 50 papers resulted appropriate for this review according to all authors.

Pathogenesis of AIED

An uncontrolled attack against inner ear antigens, resulting in both T-cell responses and autoantibody development, has been proposed as the pathogenetic mechanism of AIED.¹ This immunological process may result in cochlear and vestibular insults.⁶ The most commonly reported endocochlear damages are cochlear vasculitis, atrophy of the organ of Corti, otic capsule otospongiosis, endolymphatic hydrops and spiral ganglion degeneration.¹

To date, the onset of immune-mediated SNHL is still not a well-understood process, caused by (1) the difficulty in accessing the anatomic structures of the inner ear, by the available diagnostic tools; (2) the unreliable data obtained from peripheral blood studies and (3) the lack of an ideal animal model.¹

Data in the literature suggest that the endolymphatic sac could be primarily involved in the pathogenesis of AIED.⁷ Many antigens in the inner ear and possibly in the endolymphatic sac have been recognized as possible AIED targets.⁷ Among those, cochlin, an extracellular matrix protein specifically present in the inner ear, has been proposed as a possible cochlear antigen involved in the pathogenetic mechanism of AIED: anti-cochlin antibodies have been detected in a small cohort of patients affected by AIED and may advocate a cochlear specific antibody response.⁷

After the activation of the immune response and the release of interleukin (IL)-1 β ,⁷ the autoimmune response is promoted and the activated circulating leucocytes and immunoglobulins can target, by chemotaxis, the inner ear in response to antigenic stimuli.⁷ The activated lymphocytes cross the blood-labyrinthine barrier (probably entering the cochlea along the spiral modiolar vein of the scala tympani) and reach the endolymphatic sac.⁷ Tumour necrosis factor (TNF) is also considered a pro-inflammatory cytokine promoting the autoimmune response.⁷ The pathogenesis of AIED could be a consequence of (1)

deposition of circulating immune complexes (responsible for type III immune response); (2) vestibule-cochlear autoantibodies (responsible for type II immune response, a cytotoxic antibody mediated injury); (3) vasculitis; (4) micro-thrombosis and (5) electrochemical alterations.⁷

In order to study the role of humoral immunity in the pathogenesis of immune-mediated labyrinthitis, specific animal models have been used,⁸ characterized by high levels of circulating anti-DNA autoantibodies and immune complexes (C3H/lpr and MRL/lpr mice), with variable results.⁸

Clinical features of AIED

The clinical expression of AIED can be heterogeneous, but in most cases (80%) patients show a 30 dB, or higher, bilateral and asymmetrical SNHL.¹⁻⁴ The latter is characterized by a rapidly progressive onset over weeks or months (usually progressively developing between 3 and 90 days). The hearing deficit sometimes presents threshold fluctuations.¹⁻⁴ Frequently, in the early stage of AIED, only one ear is affected.¹⁻⁴ Particular attention has to be paid to the timing of the SNHL onset, in order to distinguish an autoimmune cochleopathy from a sudden SNHL (characterized by a sudden onset within 3 days or less) or from an age-related SNHL (presbycusis with a generally progressive late onset).¹⁻⁴

In about 50% of the AIED patients, hearing loss is also associated with vestibular symptoms, such as imbalance and motion intolerance, ataxia and positional or episodic vertigo.¹⁻⁴ In 25%–50% of cases, tinnitus and ear fullness can also be present.¹⁻⁴ In some cases, the hearing loss profile shows a conductive component (in approximately 33% of patients affected by granulomatosis with polyangiitis, a conductive hearing loss could be caused by the involvement of the Eustachian tube and/or the middle ear mucosa).¹⁻⁴ In up to 30% of cases, AIED is secondary to systemic autoimmune disease such as systemic lupus erythematosus, rheumatoid arthritis or Sjögren's syndrome Wegener's granulomatosis.

Diagnosis and treatment of AIED

Currently, there are no standardized diagnostic criteria or reliable pathognomonic tests for the diagnosis of AIED. Hence, the diagnosis of immune-mediated

cochleovestibular disorders is based on clinical symptoms, laboratory tests (demonstrating the presence in the serum of antibodies or activated T cells against inner ear antigens) and on the favourable response to immunosuppressive treatment.¹⁻⁴ A possible flow-chart to use for the diagnostic assessment of AIED disease is proposed in Table 2.

It has been stated that a clinical answer to the steroid administration could be considered a clinical diagnostic criterion for AIED; however, only a small percentage of patients (14%) is steroids responsive.¹ Laboratory tests represent another important diagnostic tool for AIED (see Table 2): serological evaluation, non-specific antigen screening test and other blood tests may highlight a possible systemic immunologic disorder or rule out conditions resembling autoimmune diseases.⁴⁻⁷ When autoimmune symptoms or signs are absent, these serologic tests show a limited value and also are very expensive; often these laboratory screenings are also performed in order to exclude other differential diagnosis (such as systemic lupus erythematosus inner ear disease, Lyme disease). However, laboratory tests should be recommended in all patients with a suspect AIED.³ Some authors also investigated cochlear specific antibodies in order to improve the specificity of AIEDs diagnosis, such as anti- β -tubulin, anti- β -actin, anti-cochlin,¹⁻⁴ but assertive data are still lacking. Also, the phenotypic analysis of peripheral blood lymphocytes has been proposed in the diagnostic approach to AIED, considering the reduced number of CD4+ and CD8+ lymphocytes in some cases.¹⁻⁴ A rheumatological evaluation is recommended, in order to manage properly a possible primary systemic autoimmune disorder, but also in order to monitor the immunosuppressive treatment.²

Mainly during the early stage of AIED which may present SNHL fluctuations, the differential diagnosis with Meniere's diseases (when associated with tinnitus, aural fullness and vestibular disorders) has to be considered.^{2,9} Essentially, AIED is a diagnosis of exclusion, suspected in case of a documented progressive SNHL, when other etiologic causes have been ruled out. For this reason, in case of idiopathic SNHL, a magnetic resonance imaging (MRI) should be performed, in order to exclude retrocochlear pathologies^{1-4,9} and possibly to study the inner ear features.¹⁰ Other differential diagnoses of AIEDs are represented by enlarged

Table 2. Possible flow-chart to use for AIED diagnosis and therapy.

Suspected AIED		
Clinical history	Audiological features	Laboratory tests
<ul style="list-style-type: none"> • Hearing loss • Rule out other predisposing known factors of SNHL (i.e. noise or ototoxic drugs exposure) • Presence of hearing loss, vestibular symptoms, tinnitus, ear fullness • Diagnosis of systemic autoimmune disease • Symptoms of autoimmune diseases 	<ul style="list-style-type: none"> • Otoscopy: unremarkable and/or non-specific; possible granulomatous otitis in some systemic autoimmune diseases (i.e. Churg–Strauss syndrome, Wegener’s granulomatosis) • Bilateral, asymmetrical SNHL of at least 30 dB or more at any frequencies developing between 3 and 90 days (possible presence of conductive component) 	<ul style="list-style-type: none"> • Complete blood count, complement proteins levels, renal and thyroid function, erythrocyte sedimentation rate, C-reactive protein levels, coagulation profile • Antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), anti-extractable nuclear antigen (ENA), anticardiolipin, anti-β2-glycoprotein I, anti-HSP70 (heat shock protein) antibodies, circulating immune complexes levels, sedimentation rate, Raji cell, rheumatoid factor, complement C1Q, smooth muscle antibodies, anti-microsomal antibodies, thyroid stimulating hormone (TSH), anti-gliadin antibodies, human leukocyte antigen (HLA) testing • anti-HIV, Lyme enzyme-linked immunosorbent assay (ELISA), fluorescent treponemal antibodies absorption test, HBAIC • Anti-β-tubulin, anti-β-actin, anti-cochlin autoantibodies • phenotypic analysis of peripheral blood lymphocytes
↓		
Possible AIED		
<ul style="list-style-type: none"> • Documented progressive SNHL • Possible hearing threshold fluctuations (threshold shift of 15 dB HL in one frequency or of 10 dB HL in two contiguous frequencies or significant change in verbal discrimination) • Steroid treatment responsiveness • Other causes of SNHL ruled out 		
↓		
Available therapies		
<ul style="list-style-type: none"> • Steroids: immunosuppressive action and electrolytes homeostasis balancing • Cytotoxic agents (methotrexate, cyclophosphamide, azathioprine), in selected cases (refer to text) • Biologic agents (rituximab), in selected cases (refer to text) • Plasmapheresis, in selected cases (refer to text) 		

AIED: autoimmune inner ear disease; SNHL: sensorineural hearing loss.

vestibular aqueduct syndrome, endocrine hypertension and Charcot–Marie–Tooth disease.^{1–4,11}

The main treatment for AIED is by corticosteroids (see Table 2). AIED is one of the few forms of SNHL which may be reversible, potentially taking advantage from a prompt medical treatment. In case of a therapeutical response and an audiometric hearing improvement at the end of 4 weeks of treatment, it has been recommended to continue the administration of steroids until clinical stabilization and then to reduce the dosage in approximately

6 months; otherwise, in non-responder patients, steroids should be reduced over a period of 10–14 days.^{2,9} According to Broughton et al.,¹² a response to the treatment is defined as positive if there is a pure tone average (PTA) improvement >10 dB and an improvement >12% in the word discrimination rate.

As already stated, not all AIED patients benefit from steroid use. Initially, about 70% may respond to the steroid therapy, but over the time the effect might decrease. Data in the literature suggest that

the estimated real efficacy of steroid treatment in only 14%.¹⁻⁴

For the AIED patients who are non-responsive to corticosteroids or who become refractory to steroids or who are intolerant to steroids side-effects, alternative immunosuppressive treatment or steroid-sparing agents have been proposed.² Cytotoxic agents (such as methotrexate, cyclophosphamide, azathioprine) have been used as possible alternative drugs, even if with limited results.¹⁻⁴ Among immunosuppressive drugs, ciclosporin A, mycophenolate mofetil and azathioprine have been proposed in small case series and to date, there are not sufficiently evidences supporting their usage on large series.¹⁻⁴ Finally, the use of biologic agents (such as rituximab) and plasmapheresis has been proposed, but these observations need additional clinical verifications.¹⁻⁴

Hearing aids have been recommended to treat hearing loss and to achieve a threshold recovery when a medical treatment is inefficient. Cochlear implantation remains the most efficient rehabilitative strategy for the AIED patients presenting profound and irreversible SNHL.¹⁻⁴

In conclusion, AIED represents a rare fluctuating progressive bilateral and often asymmetrical SNHL which usually occurs over weeks to months.² The inflammatory and the immune-mediated pathogenetic mechanisms are still not completely known, but an early AIED identification and a prompt medical treatment might result in acceptable outcomes. To date, there are no specific diagnostic tests available and the immune-mediated cochleovestibular diseases remain a challenging diagnosis of exclusion. A close collaboration between otolaryngologists, audiologists and rheumatologists is recommended in order to achieve the more suitable multidisciplinary management of this rare entity, since the early diagnostic stage, to the therapeutic and rehabilitative strategies. Patients should be followed-up with monthly audiograms if threshold fluctuations occur and then every 6 months, in consideration of the possible progressions.²

Larger cohort clinical studies are necessary in order to improve the knowledge about the etio-pathogenesis of AIEDs; a better comprehension of the molecular and intracellular pathways and of the cytokine/molecular environment involved in the cochlear damage may highlight possible new pharmacological targets for the AIED treatment.

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