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DIAGNOSTIC APPROACHES IN AUTOIMMUNE INNER EAR DISEASE: A SCOPING REVIEW OF CURRENT AND EMERGING STRATEGIES

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Abstract: In order to critically assess diagnostic methods for autoimmune inner ear disease (AIED), this review summarizes the most recent research. The goal is to examine new technologies and draw attention to the ongoing lack of a definitive diagnostic gold standard. The review examines important areas of progress, such as prospective serologic and functional biomarkers, sophisticated imaging techniques, and genetic testing, while concentrating on the shortcomings of current clinical and laboratory diagnostic criteria. The conclusion emphasizes that AIED is still a diagnosis of exclusion despite encouraging advancements, such as the study of inner-ear-specific proteins (such as cochlin and prestin) and innovative imaging techniques. Clinical presentation, documented progressive hearing loss, and a favourable reaction to immunosuppressive treatment are all necessary. The validation of certain biomarkers and the development of uniform diagnostic criteria must be the top priorities for future research in order to enable earlier and more accurate diagnosis, which will enable prompt and efficient treatment.

Keywords: Autoimmune Inner Ear Disease (AIED), Sensorineural Hearing Loss (SNHL), Corticosteroid Therapy, Biomarkers (Cochlin, Otolin-1, Anti-HSP70), Immunosuppressive Treatment, Diagnostic Techniques.

INTRODUCTION

McCabe's traditional description of AIED is bilateral sensorineural hearing loss that progresses quickly (over weeks to months) and reacts to immunosuppressive medication. Primary AIED is a rare condition [1]. The exact incidence of AIED is unknown since there is currently no reliable diagnostic test for the condition. However, the rate of abrupt sensorineural hearing loss is higher, occurring in one instance per 5,000 to 10,000 people annually, making it less prevalent [2]. The condition appears to be more prevalent in women aged 20 to 50 and is characterized by a fast-progressive, frequently fluctuating bilateral sensorineural hearing loss (SNHL) that develops over a few weeks to months [3]. Rheumatoid arthritis, disseminated vasculitis, Sjögren's syndrome, polychondritis, myasthenia gravis, Hashimoto's thyroiditis, Cogan's syndrome, Behçet's disease, sarcoidosis, Wegener's granulomatosis, and systemic lupus erythematosus are among the systemic autoimmune illnesses that coexist in 15–30% of patients. recurrent polychondritis with colitis ulcerosa. [4]

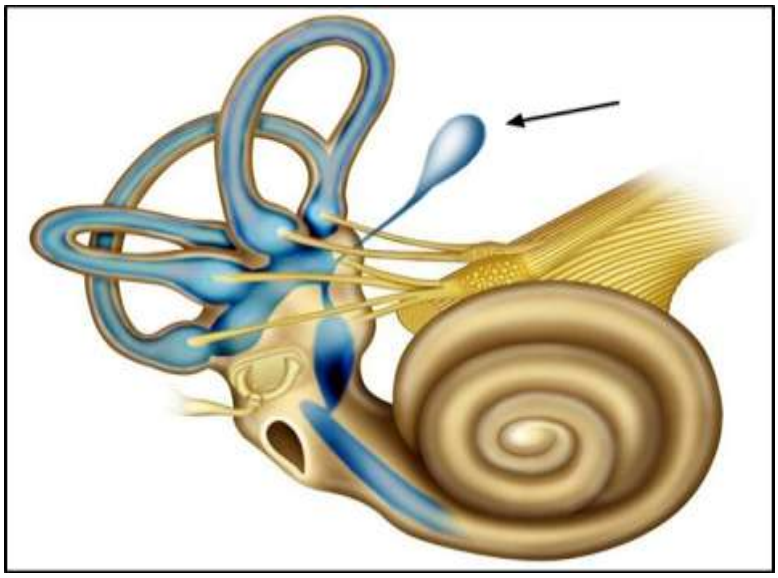

Figure 1: Autoimmune Inner Ear Disease (AIED) can originate in the endolymphatic sac (black arrow)

In the late 19th and early 20th centuries, the idea of autoimmune disorders started to take shape when conditions like systemic lupus erythematosus (SLE) and rheumatoid arthritis were observed, where it was thought that the body's own tissues were being attacked by the immune system. The finding of antinuclear antibodies (ANAs) in lupus patients was one of the seminal discoveries made in the mid-1900s that shed light on the autoimmune nature of some illnesses. Additionally, around this time, diagnostic assays to identify

these antibodies were developed. [5, 6] The finding of inner ear-specific autoantibodies in the sera of patients with AIED, its co-occurrence with other autoimmune disorders, and its positive response to immunosuppressive medications all lend credence to an autoimmune-mediated mechanism, according to current literature. Clinical evaluation, SNHL demonstration with recurring audiologic testing, and immunomodulatory medication response are used to make the diagnosis of AIED, which is an exclusionary diagnosis. [7, 8] There is no definitive and generally recognized marker for the diagnosis of AIED, despite the fact that a number of them have been reported, and the current laboratory tests are contentious. [9, 10] Although its usefulness has been disputed, the antibody to Heat Shock Protein-70 is the most commonly reported marker in AIED. [11, 12]

Autoimmune disease prevalence varies greatly; some estimates place the total number of affected individuals in affluent nations between 5 and 8%. Genetic predisposition, environmental variables, and shifts in diagnostic standards and knowledge can all have an impact on the frequency and prevalence of particular autoimmune illnesses, which can vary over time. [13, 14]

RESEARCH METHODOLOGY

1.1 Search Method

A comprehensive search of the literature, including publications published between January 2020 and December 2024, was carried out in the databases MEDLINE, INSPEC, and Web of Science Core Collection. Boolean operators were used to broaden or narrow the search parameters, which included "autoimmune inner ear disease" AND "diagnosis." The following were the requirements for inclusion:

1] Peer-reviewed papers released from January 2020 to December 2024;
2] Research on diagnostic approaches, such as genetic markers, imaging methods, or sophisticated AIED testing;
3] English-language publications. [15]

According to the Systematic Reviews and Meta-Analyses (PRISMA) declaration, this study was in compliance. Relevant papers from 2011 to December 2021 were found using the Scopus, PubMed, ISI, Google Scholar, and Cochrane Library databases. The following keywords were applied to the remaining databases: multiple sclerosis, vitiligo, autoimmune illnesses, systemic lupus erythematosus, rheumatoid arthritis, sensorineural hearing loss, abrupt hearing loss, and inflammatory bowel disease. [16] The full text of the remaining articles was assessed for subject inclusion criteria, number of subjects, treatment type and duration, audiologic and vestibular evaluations, blinding, randomization, and follow-up. After review articles, animal studies, and other publications lacking information about outcomes following treatment for AIED were removed. Final inclusion was restricted to studies that reported outcome data for AIED participants receiving any kind of treatment other than oral steroids alone, with a focus on data that was gathered prospectively. [17]

1.2 Inclusion and Exclusion Criteria

Controlled clinical trials, randomized controlled trials, and prospective and retrospective cohort studies are the requirements for inclusion. This article did not include case reports, reviews, in vitro experiments, or case studies. [16]. For this review, the following criteria had to be met: (a) studies that treated AIED with audiometric data on hearing outcomes; (b) studies that were either prospective or retrospective in nature; and (c) studies that were published between April 1990 and April 2020. Based on trends in AIED research, dates were chosen. The following were excluded: (a) case reports; (b) studies with fewer than four participants; and (c) studies that used subjective hearing monitoring without audiometric data. [18, 19]

1.3 Data Extraction

A systematic data extraction process was used to record important information about the diagnostic techniques investigated, such as their corresponding clinical impacts, specificities, and sensitivities. To maintain uniformity and reduce potential bias, a standardized data extraction template was used during the extraction procedure. To integrate and condense the results, a narrative synthesis approach was used. [15] Audiometric data, treatment mode, study design, sample size, and reported vestibular symptoms were among the information that was retrieved. Hearing improvement was the main result, and vestibular symptoms were the secondary result. Significant variation existed between studies in the methods used to evaluate the results of primary and secondary research. Instead of combining the findings from all the studies, a qualitative comparison was done. [18, 19] The research was solicited by two writers (LX and ZC). [16]

CURRENT DIAGNOSTIC APPROACHES

Reliable pathognomonic testing and standardized diagnostic criteria are currently lacking for the diagnosis of AIED. Immunomodulated cochleovestibular illnesses are therefore diagnosed based on clinical symptoms, laboratory testing [which shows that antibodies or activated T cells against inner ear antigens are present in the serum], and the positive response to immunosuppressive therapy. To exclude retro cochlear diseases, a magnetic resonance imaging (MRI) assessment should be conducted for SNHL [20]. The Rauch criteria, which include "bilateral sensorineural hearing loss of at least 30 dB at any frequency and evidence of progression in at least one ear on two serial audiograms performed three months apart," can be used to suspect AIED in pure tone audiograms. [21]. Primary AIEDs can be challenging to diagnose. As of yet, neither immunologic nor serologic testing has proven to be accurate enough to provide a conclusive diagnosis. [22]. To summarize, the diagnosis of primary AIED is made based on clinical evaluation, the presence of progressive sensorineural hearing loss on monthly audiometric assessments, and above all a favorable reaction to corticosteroid therapy. The diagnosis might be supported by the existence of a positive Western blot. [23] Since there is now substantial evidence that immunological pathways play a role in the aetiopathogenesis of inner ear damage, none of the tests that have been suggested for the diagnosis of AIED are practical or effective in clinical settings as of this writing. [24]

2.1 Clinical Diagnosis-

It can be distinguished from a number of other diagnostic options by its advancement over the course of days to months. [25] As a result, autoimmune inner ear disease is still determined by exclusion rather than by positive results. Many times, the presence of concurrent autoimmune disorders, such as systemic lupus erythematosus, Cogan's syndrome, and others, can be used to identify patients

who present with autoimmune inner ear disease. [25, 26-28] Although they are not a diagnostic indicator for autoimmune inner ear disease, their co-occurrence with inner ear illness should encourage the doctor to move forward with an immunological laboratory workup. Lastly, the clinical manifestation of Meniere's disease can be similar to that of autoimmune inner ear disease [29, 30].

2.2 Laboratory Diagnostic Evaluation-

While none of the laboratory tests for autoimmune inner ear disease are completely sensitive or specific, they are all generally helpful predictors of how well corticosteroid therapy will work [31, 32]. Antigen-specific or antigen-nonspecific assessments of immune function are the two categories of laboratory tests used to identify the disease. [32, 31] On the other hand, only a few research labs offer antigen-specific procedures such as the lymphocyte transformation test, the migration inhibition assay, indirect immunofluorescence, and Western blot analysis of cochlear antigens. These tests seem to be helpful in determining which patients will benefit from steroid treatment. Despite having excellent sensitivity and specificity, they are not perfect. [33, 32] In these patients, a corticosteroid trial is necessary. [25, 32]

2.3 Response to Corticosteroid Therapy

In order to diagnose autoimmune inner ear disease, the third requirement is a favorable response to corticosteroid therapy. A test of corticosteroid treatment or corticosteroid and cyclophosphamide treatment is part of it [29, 25, 34]. A corticosteroid treatment that reverses or stabilizes the hearing loss validates the probable diagnosis. [26].

EMERGING DIAGNOSTIC APPROACHES

The diagnosis of AIED necessitates a thorough evaluation of the patient's situation because there is no gold standard. In line with the higher incidence of autoimmune illnesses in women, AIED is somewhat more prevalent in women than in men. Usually, onset occurs between the ages of 20 and 50. [35]

3.1 Biomarkers and Autoantibodies

The biomarkers that were found were also categorized according to their clinical use, which included pathologic, prognostic, and diagnostic. The original publications found 55 molecular (Table 1) and 10 functional biomarkers (Table 2) associated with inner ear pathology, in addition to numerous other biomarkers that were mentioned in passing in review articles (Table 3). [36].

Biomarker Classification—Three of the functional biomarkers were predictive, two were prognostic, and seven were diagnostic. Based on the reviewers' determination of whether or not the study achieved its own predetermined goals, we established another classification.

3.1.1 Molecular Biomarkers (Tables 1 and 3)

Protein Biomarkers Particular to the Inner Ear that Are Detectable in Serum, Plasma, or Peripheral Blood

Protein Biomarkers

a) Mulry and Parham contained a thorough explanation of the functions of protein biomarkers. The proteome study made it possible to identify a large number of distinct inner ear proteins, some of which are present specifically within the inner ear and others of which can be detected in peripheral blood. Otolin-1, prestin, and matriline are the proteins that can cross the blood-labyrinthine barrier and be found in the blood.

b) Otolin-1 is a 70 kDa glycoprotein that is connected to the tectorial membrane and inner ear sensory hair cells. Drilling time positively correlates with significantly elevated levels in inner ear damage cases in mastoidectomies, demonstrating its role. [37] Sacks and Parham discovered a profound association between osteoporosis, benign paroxysmal positional vertigo (BPPV), and otolin-1 levels. [22]

c) Prestin is a cochlear outer hair cell (OHC) motor protein that weighs 80 kDa. One possible sign of OHC damage is the presence of prestin in serum. This was initially proposed by Parham while researching the hearing loss in Wistar rats brought on by noise exposure. In cases of ISSHL with successful treatment and hearing threshold restoration, this latter study also proposed the predictive significance of lowering prestin levels.

d) Matrilin-1 is a 148 kDa protein that is exclusive to cartilage and is mostly found in the tracheal and nasal cartilage of the upper airways. It has been shown to correlate with cartilage inflammation and can be identified in the serum of patients who have recurrent chondritis (RC).

3.1.2 Biomarkers of Inflammation

Antibody Biomarkers

a) Anti-type II collagen antibodies—According to Arnaud *et al*., 33% of patients with recurrent polychondritis have antibodies against type II collagen in their blood.

b) Antinuclear antibodies (ANA)—Patients suffering from Meniere's disease (MD) have ANA blood titers that are 21–28% higher. [37] Additionally, blood levels of anti-U1RNP, antiendothelial cell, and IgG-type anticardiolipin antibodies were higher in patients with mixed connective tissue disease (MCTD) who experienced sudden sensorineural hearing loss [SNHL] than in individuals with MCTD who did not. Patients with MCTD who had SNHL had higher serum levels of interferon γ and tumor necrosis factor-α than those who did not, but they also had fewer natural regulatory T cells (CD4 + CD25) overall. [38] However, 15–30% of patients suffering from a bilateral progressive sensorineural hearing loss, which may be autoimmune inner ear disease (AIED), may also have another autoimmune disease at the same time [39]. There was no relationship between the age or length of MCTD onset and the estimated 46.4% of MCTD patients who had SNHL, according to Hajas *et al*. [39] Other antibodies, such as anticardiolipin (aCL) or anti-endothelial cell antibodies (AECA), may influence the clinical manifestations and the progression of the disease. Antinuclear antibodies and anti-U1RNP were identified as characteristic of the disease. [40, 41] Factor H and B, fibrinogen α and γ, β actin, and pigment epithelium-derived factor proteins were all overexpressed in plasma samples taken from MD patients, according to profiling. [42] At the same time, apolipoprotein I, vitamin D binding proteins, and β-2 lipoprotein I were all under expressed in comparison to controls.

Additional research is required for confirmation because of the small sample size. [43]. A high number of white blood cells (WBC) was uncommon in their cohorts, they discovered, although erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) indicated disease activity and response to treatment. [44] Haasse and Prassad verified the significance of C-reactive protein (CRP) and updated the inflammation biomarkers by adding cytokines (TNF-α & interleukin-6) and enzymes (synthase). [45] They also underlined how important IL-6 is as a proinflammatory cytokine. [46] Despite the initial assumption that anti-phospholipid antibodies were involved in the activation of microthrombi formation in the inner ear in instances with SSNHL [47], none of the 60 patients in the study by Süslü *et al*. showed anti-phospholipid IgM or IgG antibodies [48].

3.1.3 Antiviral Antibodies

Antibodies to CMV, herpes zoster, herpes simplex type 1, influenza B, and mumps were detected in the serum of patients with idiopathic abrupt deafness. The direct relationship between the viral infection and hearing loss is unclear, though, as there was no correlation between the antibody titer and hearing loss, and the Henle–Koch postulates could not be met.

3.1.4 Other Biomarkers

a) Complement factor H contributes to the alternative complement activation pathway as a glycoprotein. But age-related macular degeneration, hemolytic uremic syndrome, and membranoproliferative glomerulonephritis were all associated with a mutation in a gene that codes for complement factor H. Additionally, it was higher in cases of otitis media with effusion, which was recently linked to MD [37].

b) Beta-2 glycoprotein 1 (beta-2GP1) is an additional glycoprotein that interacts with phospholipids on the surface of injured cells to bind to negatively charged molecules (heparin, dextran sulfate) and stop the intrinsic blood coagulation cascade from activating. Recently, autoantibodies that target beta-2GP1 have been found in sensorineural hearing loss patients.[49]

c) Beta-actin is a structural protein that is necessary for the integrity of the cytoskeleton and for the stereocilia's structure in hair cells. Mutations that may change the polymerization of actin filaments in the cytoskeleton and other organelles have been linked to both dystonia with nonsyndromic hearing loss and autosomal dominant hearing loss.

d) Vasopressin is a hormone that controls the osmotic pressure of body fluids. Higher amounts of vasopressin were found in the acute stage of Meniere's disease, according to retrospective research. This matches the findings of Kumagami *et al*., who suggested that the release of vasopressin may cause a vertigo attack in Meniere's illness by reducing fluid reabsorption in the endolymphatic sac and causing endolymphatic hydrops in guinea pigs. Another investigation on animals showed that when inner ear pressure is compressed, plasma vasopressin levels drop.

e) Vitamin D binding protein (VDBP) acts as a scavenger of actin, shielding cells from the harmful effects of intravascular actin polymerization. It is also referred to as Gc-globulin (group-specific component globulin). In terms of mechanism, VDBP has been demonstrated to decrease platelet aggregation and increase the ex vivo coagulation time.

f) Glucocorticoids and brain-derived neurotrophic factor (BDNF) have been supported by Rüttiger and colleagues. The concentration of BDNF in human serum is significantly higher (factor of 200) than in human plasma, and it has been more closely associated with tinnitus and hyperacusis.

3.1.5 Inner-Ear-Specific Biomarkers Detected in the Perilymph or Inner Ear Structures

a) Cochlin is a protein that is expressed in the vestibule and cochlea [37], and it plays a significant role in the diagnosis of perilymphatic fistula. Its sensitivity and specificity are 100% and 86.4%, respectively. [50] Additionally, it was discovered that autoimmune inner ear disease and MD [51] both overexpress cochlin [52]. Cochlin was consistently found in the crista ampullaris, utricle, or perilymph, despite evidence of its function. Along with otospiralin [53], otoraplin [37, 54], and oncomodulin, other proteins that may be present in the inner ear include prestin, otoancorin, otogelin, α-tectorin, β-tectorin, and otoconin-90.

b) Heat shock proteins [HSP] belong to a family of cytoplasmic chaperone proteins that control how other proteins fold. Pennisi *et al*. found that HSP90 is a crucial chaperone protein that plays a role in stress responses. [37] It is HSP90 that is necessary for protein maturation, not de novo protein folding. Schmitt *et al*.'s observational investigation of heat shock proteins in 39 perilymph samples taken during ear surgery brought to light the challenge of getting control individuals to provide perilymph samples. [55] The similar difficulty was observed when staining for the monocyte-macrophage biomarker 27E10 in temporal bone studies of the sensorineural consequences of chronic otitis media. The scala tympani was proposed by Jókay *et al*. as the site of lymphocyte-macrophage interaction, generating SNHL, despite difficulties with sample accessibility. [56]

3.1.6 Biomarkers of Oxidative Stress (Damage)

Haase and Prassad examined antibodies against cardiolipin and Saccharomyces cerevisiae [ASCA], and they categorized oxidative stress biomarkers into three categories: protein modification [3-nitrotyrosine protein carbonyls], DNA adduct [8-hydroxydeoxyguanosine], and lipid peroxidation [including malondialdehyde and F2-isoprostane]. [45] Since free radical activity is reflected in NIHL, malondialdehyde, 4-hydroxynonenal, nitrotyrosine, and inducible NO synthase [iNOS] are among its stress indicators. [57] Apoptosis may also be mediated by other proteins, like cytochrome C, and enzymes, like caspases, which may contribute to the degeneration of auditory nerve fibers. The two-hit mechanistic response of idiopathic sensorineural hearing loss is cochlear ischemia followed by reperfusion damage. [37] Increased levels of several biomarkers, such as malondialdehyde, which shows the activity of free radicals, are seen in the cochlea in cases of drug-induced ototoxicity. While endogenous antioxidants like glutathione and antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase are reduced in levels, the transcription factor nuclear factor-erythroid 2-related factor-2 (Nrf2), which is a key regulator of antioxidant enzyme expression, protectively increases these enzymes against ototoxicity. [58] In animal models of injury to vestibular hair cells, there is an increase in the production of NF-kB and proinflammatory steroids. [59]

3.1.6 Functional Biomarkers (Table 2 and 3)

Event-related potential P1, N1, and P2 Complex (CAEP). The event-related potential for auditory neuropathy spectrum disorders was the emphasis of Campbell *et al*., whereas Mostafa *et al.* attempted to use it as a measure of improved amplification when comparing cochlear implants with hearing aids. [37] Brainstem auditory evoked responses (ABR). The primary three waves, I, III, and V, of the ABR have been shown to be a reliable biomarker for sensorineural hearing loss brought on by lead poisoning, according to Counter and Buchanan. [60] Dewey assessed the effects of noise exposure and concluded that fMRI was a useful addition to the ABR. The I/V amplitude ratio was employed as a biomarker on the ABR side for both low and high noise exposure groups [61].

a) Functional magnetic resonance imaging (fMRI). In children with hearing loss who had cochlear implants before the age of 36 months, Deshpande *et al*. discovered a relationship between post-cochlear implant speech language-auditory performance and the activation of the angular gyrus, supramarginal gyrus, middle temporal gyrus, precuneus, medial frontal gyrus, orbital gyrus, cingulate gyrus, subgyral, and middle occipital gyrus. [61].

b) A temporary threshold shift (TTS). To forecast how long a person would be exposed to noise, Moshammer *et al*. used the TTS. It was suggested that OAE suppression by contralateral activation of the medial olivocochlear reflex was a predictor of workers' susceptibility to NIHL. OAE measurement enables the functional evaluation of the OHCs, which are the main targets of NIHL.

c) Electrovestibulography (EvestG). Even though Garrett *et al*. came to the conclusion that separating the reaction into acceleration and deceleration would help differentiate between Meniere's disease and Benign Paroxysmal Positional Vertigo [BPPV], the findings indicated that the DC component merits more investigation. [37].

Table 1. Molecular biomarkers related to the inner ear in humans.

Author	Year	Study Type	Level of Evidence	Met Objectives	Biomarker	Key Source	Category	Ref
Archibald *et al*.	2010	Blind retrospective chart review	3b	Yes	B7-H1 expression in lymphocytes	Fresh frozen vestibular schwannoma Tissue	Diagnostic	[37]
Edvardsson Rasmussen *et al*.	2018	Observational	4	Yes	Alpha-2-HS-Glycoprotein	Perilymph aspirated through round window membrane	Prognostic	[37]
Schmitt *et al*.	2018	Observational	3b	Partially	Heat shock proteins	Perilymph & Cochl. T	Diagnostic	[55]
Lee *et al*.	2017	Observational	1b	Yes	Autoimmunity; elevated sera CRP & ESR in addition to many other proteins specific for autoimmune inner ear disease, or sudden SNHL	Blood	Diagnostic	[10]
Kim *et al*.	2014	Prospective correlational	3b	Partially	Neuro-immunology antigens involved in immune Reactions	Endolymphatic sac luminal fluid from 3 patients & peripheral blood from 10 patients	Diagnostic	[37]
Betancur *et al*.	2018	Prospective correltional	1b	Yes	Anti-centrosome antibodies, MSA-2 CENTP-F/MSA-3, Nu-MA/MSA-1	Serum	Diagnostic	[48]
Hajas *et al*.	2009	Prospective correltional	2b	Partially	T cell count, IgG antibodies Anti-endothelial cell antibodies [AECA]; High	Plasma & Serum	Diagnostic	[38]

					levels of anti-U1RNP, IgG type aCL & AECA			
Ikezono *et al.*	2018	Prospective correlational cohort	2b	Yes	Perilymph-specific protein Cochlin-tomoprotein [CTP]	MEL [Middle ear lavage] & Peripheral blood [Plasma & Serum	Diagnostic	[50]
Berti *et al.*	2013	Observational study	3b	No	Inner ear autoantibodies	Serum	Prognostic	[37]
Sacks & Parham	2015	Prospective pilot clinical trial	2b	No	Otolin-1	Serum	Diagnostic	[37]
Haase & Prasad	2016	Research guidance papers	1a	Yes	Biomarkers of oxidative stress; biomarkers of inflammation	Peripheral blood	Diagnostic	[45]
Aoki *et al.*	2007	Retrospective cohort	2b	No	Plasma osmolality; plasma Vasopressin levels	Plasma	Diagnostic	[37]
Parham *et al.*	2014	Retrospective controlled cohort	3b	No	Otolin-1	Serum	Diagnostic	[37]
Jókay *et al.*	2001	Retrospective observational	2b	Yes	Staining for 27E10 in chronic otitis media	Temporal bones from autopsies	Pathogenic	[56]
Hansen & Linthicum	2004	Retrospective observational	4	Yes	ERB2 & E3, Neuregulin	Pathological specimens of vestibular schwannoma	Diagnostic	[37]
Chiarella *et al.*	2012	Cohort	2b	Partially	Beta 2 glycoprotein, beta actin, complement factor-H, vit. D binding protein	Plasma	Diagnostic	[43]

Table 2. Functional biomarkers related to the inner ear in humans.

Author	**Year**	**Study Type**	**Level of Evidence**	**Met Objectives**	**Biomarker**	**Category**	**Ref**
Mostafa *et al.*	2014	Correlational cohort	1b	Partially	P1 CAEP	Diagnostic	[37]
Dimitrijevic	2016	Correlational thesis	2b	No	Envelope following response	Diagnostic/ Prognostic	[37]
Counter & Buchanan	2002	Correlational	2b	No	Brainstem Auditory evoked responses	Diagnostic	[60]
Campbell	2011	Descriptive	4	No	P1 component of the cortical auditory evoked potential	Treatment	[37]
Dewey *et al.*	2018	Observational	1b	No	Regions of Interest [ROIs] on fMRI	Diagnostic	[37]

Feuerstein *et al.*	2015	Observational	5	No	Temporal Threshold Shift [TTS]	Predictive	[37]
Moshammer *et al.*	2015	Pre- and post, correlational	1c	Yes	Temporal Threshold Shift [TTS]	Diagnostic	[37]
Coffey *et al.*	2016	Prospective observational	2b	Yes	Auditory Frequency Following Response [FFR]	Diagnostic	[37]
Choi *et al.*	2017	Secondary analysis of a double-blinded randomized clinical trial	2b	Yes	Electrode impedance fluctuations	Prognostic	[57]
Deshpande *et al.*	2016	Prospective correlational	1b	Yes	Preoperative fMRI activation in angular and cingulate gyri and prefrontal cortex	Predictive	[61]

Table 3. Review article of biomarkers related to the inner ear.

Author	Year	Level of Evidence	Met Objectives	BioMarker	Key Source	Classification	Category	Ref
Evans & Halliwell	1999	2a	Yes	Reactive oxygen and nitrogen Species	Review of intracellular & extracellular antioxidants	Molecular	Pathophysiology/ Therapeutic	[37]
Arnaud *et al.*	2014	2a	Partially	CII Ab & cell immunity in relapsing polychondritis	Review of immunity in serum	Molecular	Pathogenic model	[37]
Okano	2014	5	Too broad	Immune markers	Review of immunity in serum	Molecular	Pathophysiology/ Therapeutic	[37]
Alawieh *et al.*	2015	1a	Yes	Biomarkers of inflammation	Review of immunity in plasma	Molecular	Diagnostic	[37]
Barozzi *et al.*	2015	2a	No	Inner ear melanocytes	Review of aggregated inner ear melanocytes papers	Molecular	Diagnostic	[37]
Rüttiger *et al.*	2017	5	Yes	Overview of both functional & molecular [e.g., BDNF]	Evoked potentials + Aggregated IHC & OHC biomarkers in animal & human studies	Functional and Molecular	Diagnostic/ Pathognomonic	[37]
Mulry & Parham	2020	2a	Yes	Inner ear/preclinical models: [Otoconin 90/95, Otogelin, Otoancorin, Cochlin, α-tectorin, β-tectorin.] Vestibular biomarkers: Cochlin & Otolin-	Review of aggregated data of proteins specific to the inner ear, some of which could be detected outside the inner ear	Molecular	Diagnostic	[37]

3.2 Imaging Evaluation

The assessment of AIED's impact on the inner ear has greatly improved because of developments in imaging technologies. Both computed tomography (CT) and magnetic resonance imaging (MRI) are essential diagnostic tools, particularly when clinical symptoms are similar to those of other hearing loss causes. Even while cochlear enhancement on MRI is not unique to AIED, it can be a sign of inner ear inflammation that is compatible with the condition. MRI with intratympanic gadolinium enhancement has demonstrated promise in identifying inflammatory alterations and visualizing inner ear structures. Moreover, when inner ear pathology is suspected, gadolinium [Gd]-enhanced MRI with 3D fluid-attenuated inversion recovery (FLAIR) imaging is especially helpful. By aiding in the differentiation of AIED from other illnesses, these imaging approaches not only improve diagnostic precision but also enable earlier detection and customized therapies.

3.3 Genetic Testing

Finding susceptibility factors for AIED through genetic testing has been increasingly useful, especially in instances with idiopathic or familial clustering. [62]. Notably, some haplotypes of the human leukocyte antigen (HLA), such as HLA-B27, B35, B51, C4, C7, and A1-B8DR3, have been studied for their possible use as prognostic indicators in hearing loss associated with AIED. [24-30] Furthermore, a higher risk of sudden SNHL has been linked to genetic variations in the interleukin-1 receptor (IL-1R) genes. Genetic testing helps with risk assessment, provides important insights into disease causes, and guides individualized treatment plans by detecting genetic predispositions.

3.4 Diagnostic Therapy

The ability to respond to steroid treatment is seen as a crucial clinical factor in the diagnosis of AIED. Treatment's backbone, corticosteroids, are frequently utilized as a diagnostic and therapeutic technique. A good response might aid in the diagnosis's confirmation; these responses are usually characterized by better hearing and fewer vestibular problems. The danger of relapse after reducing steroids and the diversity in treatment response, however, make it difficult to use this method alone for diagnosis. According to certain research, steroid therapy is 14–70% successful. [62]

TREATMENT

The first step in treatment should be a one-month steroid challenge at a daily maximum of 60 mg at 1 mg/kg. After reaching a plateau of recovery, steroid responders are reduced over eight weeks to a maintenance daily dose of 10 to 20 mg for roughly six months. They are then kept on full-dose therapy with monthly audiometry. Nonresponders are patients who do not improve after the 4-week steroid challenge, and they are eased off of steroids during a 12-day period. [63] When opposed to systemic administration, intratympanic therapy has two major advantages: it includes localized direct drug delivery to the afflicted site and creates much larger levels of steroids in the perilymph. It has also been demonstrated to improve hearing in people who are refractory to steroids. Combined with rheumatology, biologic or other immunosuppressive medication should be started if hearing loss persists after systemic and intratympanic steroids. With daily injections, 70% of steroid-resistant patients reported improved hearing, demonstrating the potential effects of the IL-1β antagonist anakinra. According to these authors, anakinra should be taken into consideration as a possible therapy option for patients who do not pass the one-month steroid challenge because of the encouraging early data, supporting biochemical evidence, and dearth of alternative treatment choices. [64] The standard starting dose for oral prednisolone is 60 mg [1 mg/kg/day], and it should be taken for at least four weeks. [65] It should be maintained and decreased gradually over a period of six months if hearing improves. After four weeks, tapering is carried out over a period of twelve days if no improvement is observed [66]. Patients who are resistant to intratympanic dexamethasone can benefit from intratympanic methylprednisolone, which was reported to have the highest concentration in the perilymph when compared to hydrocortisone and dexamethasone. Nowadays, these medications are taken in conjunction with steroids to lessen the negative effects of high doses of steroids. Steroid nonresponders are also treated with these as an option. An effective way to raise the hearing threshold is using anakinra. [67] A time-tested treatment option, corticosteroids are to be initiated as the first line of treatment and maintained for at least four weeks prior to tapering. Between 50 and 70 percent of cases respond to steroids. [66].

In situations where high doses of steroids are prohibited or when hearing loss recurs during the maintenance or steroid weaning period, adjuvant therapy with immunosuppressive drugs may be suggested. Steroid-resistant AIED is difficult to treat, and there are currently no accepted standards for doing so. Eliminating circulating antibodies, antigens, immune complexes, and other immunological mediators from the blood is the function of plasmapheresis in AIED. As an adjuvant treatment for primary AIED patients with elevated antibody titers or secondary AIED patients with coexisting systemic autoimmune illness, plasmapheresis may be useful in steroid-resistant instances. [67] For adults, the first course of treatment is a 4-week therapeutic trial of 60 mg of prednisone per day. Patients who do not respond to steroid treatment are quickly weaned off of the medication over a period of one to ten days. During a one-month period, patients who do react to treatment are tapered more gradually. [68] Typically, the first treatment trial for prednisone involves an oral dose of 1 to 2 mg/kg/d for 4 weeks. Patients who show improvement should continue for an additional 1-2 months before a gradual taper is implemented. Due to the substantial morbidity linked to prolonged systemic steroid use, transtympanic steroid injection is becoming more and more popular as a therapy option. Potential benefits include the absence of systemic levels with elevated cochlear fluid levels and ease of administration. [69] It has also been discovered that methotrexate, a folic acid antagonist, is an effective treatment with fewer possible long-term systemic side effects than steroids [70]. One possible treatment option is plasmapheresis, particularly if hearing loss persists after the use of the most effective medicinal treatments. [71]

FUTURE DIRECTION

Finding more precise biomarkers and creating standardized diagnostic standards should be the top priorities of future studies. By combining proteomic, metabolomic, and genomic research, new diagnostic indicators may be found and a deeper understanding of the pathophysiology of AIED facilitated. Further improving diagnosis accuracy may also be possible by developing imaging methods and investigating the function of immune profiling. The validation of these methods and the establishment of consensus guidelines for the

diagnosis and treatment of AIED depend on cooperative, multicenter investigations. [62] In order to create a more dynamic and individualized treatment plan for every patient, mobile tablet audiometry—using an iPad audiometer—has become a dependable method of tracking a patient's clinical development over time. [64]

CONCLUSION

A clinical diagnosis of exclusion is essential to the diagnosis of autoimmune inner ear disease (AIED), which is still a complicated and difficult disorder. No one pathognomonic test has gained widespread acceptance despite substantial research into serologic biomarkers, sophisticated imaging, and genomic profiling. Progressive sensorineural hearing loss, ruling out other causes, and a favorable reaction to corticosteroid treatment are still the three criteria used to make the current diagnosis. Significant limitations in our knowledge of its pathogenesis are highlighted by the variability of suggested biomarkers and inconsistent treatment outcomes. In the future, it will be crucial to develop precise, confirmed diagnostic criteria and find trustworthy biomarkers using integrated multi-omics techniques. In order to incorporate these new diagnostic techniques into clinical practice, further cooperative, multicenter research is crucial. This will eventually allow for earlier intervention and enhance long-term patient outcomes.

Future initiatives ought to concentrate on:

- Creating uniform diagnostic standards,
- Confirming particular biomarkers by multi-center research,
- Using multi-omics techniques to identify disease processes,
- Create tailored treatments with better safety records.

ABBREVIATIONS

- AIED – Autoimmune Inner Ear Disease
- SNHL – Sensorineural Hearing Loss
- SLE – Systemic Lupus Erythematosus
- ANAs – Antinuclear Antibodies
- PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- MRI – Magnetic Resonance Imaging
- CT – Computed Tomography
- Gd – Gadolinium
- FLAIR – Fluid-Attenuated Inversion Recovery
- HLA – Human Leukocyte Antigen
- IL-1R – Interleukin-1 Receptor
- BPPV – Benign Paroxysmal Positional Vertigo
- OHC – Outer Hair Cell
- RC – Recurrent Chondritis
- MD – Meniere's Disease
- MCTD – Mixed Connective Tissue Disease
- aCL – Anticardiolipin Antibodies
- AECA – Anti-Endothelial Cell Antibodies
- WBC – White Blood Cells
- ESR – Erythrocyte Sedimentation Rate
- CRP – C-Reactive Protein
- TNF-α – Tumor Necrosis Factor Alpha
- CMV – Cytomegalovirus
- BDNF – Brain-Derived Neurotrophic Factor
- HSP – Heat Shock Proteins
- ASCA – Anti-Saccharomyces cerevisiae Antibodies
- iNOS – Inducible Nitric Oxide Synthase
- Nrf2 – Nuclear Factor Erythroid 2–Related Factor 2
- CAEP – Cortical Auditory Evoked Potential
- ABR – Auditory Brainstem Response
- fMRI – Functional Magnetic Resonance Imaging
- TTS – Temporary Threshold Shift
- OAE – Otoacoustic Emissions
- NIHL – Noise-Induced Hearing Loss
- EvestG – Electrovestibulography
- FFR – Frequency Following Response
- ROIs – Regions of Interest
- CTP – Cochlin-Tomoprotein
- OCEBM – Oxford Centre for Evidence-Based Medicine

References

[1] Ruckenstein MJ [2004] Autoimmune inner ear disease. Curr Opin Otolaryngol Head Neck Surg 12:426–430

[2] Byl F: Thirty-two cases of sudden profound hearing loss occurring in 1973; incidence & prognostic findings. Trans Am Acad Ophthalmol Otolaryngol 1975, 80: 290-305.

[3] Hughes G, Kinneys, Barna B, Calabresa L, Hamid M [1983] Autoimmune reactivity in Ménière's disease: preliminary report. Laryngoscope 43:410-417

[4] The diagnosis of autoimmune inner ear disease is evidence of critical pitfalls. Roberto Bovo. Andrea Caroba and Alessandro Martini.

[5] Rose NR predicts & prevents autoimmune disease in the 21st century: A review & preview. AmJ Epidemiol. 2016; 183 [5]: 403-406, doi: 10.1093/aje/kwv 292

[6] Wang L, Wang Fs, Gershwin ME Human autoimmune diseases: a comprehensive J Intern Med update 2015; 278 [4]:369-395] doi: 10.1111/joim.12395

[7] Maccabe BF, Autoimmune Sensorineural Hearing Loss. Ann otol Rhinol laryngol, 2004; 113 [7]; 526-520

[8] vambutas A, Pathak S, AAQ; autoimmune and autoinflammatory [disease] in otology, what is new in immune-mediated hearing loss, laryngose investig Otolaryngol, 2016; 1 [5]; 110-115

[9] Migovic T, Zeitouni A, Colmegna, Autoimmune Sensorineural Hearing Loss: The Otology-Rheumatology Interface. Rheumatol [UK]. 2013; 52 [5]: 780-789

[10] Kommareddi PK, Nair TS, Vallurupali M, *et al*. Auto-antibodies to recombinant human CTL2 in autoimmune hearing loss. Laryngoscope 2009; 119[5]:924-932

[11] Yeomk, Gray J, Nair Ts, *et al*. Antibodies to HSP-70 in normal donors & autoimmune hearing loss patients. Laryngoscope: 2003; 113 [10] 1770-1776.

[12] Garcia Berrocal JR, Ramirez-Camocho R, Arellano B, Vargas JA. Validity of the Western blot immunoassay for heat shock protein-70 in associated isolated immunorelated inner ear disease. Laryngoscope 2002; 112[2]; 304-309

[13] Caof, 194 VC, NiQy, *et al*., on the temporal trends of prevalence of autoimmune disease from 1990 to 2019. Autoimmune Rev 2023; 22 [8]: 103359. doi: 10.1016/j.autrev 2023.103359

[14] Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases; improved prevalence estimates & understanding of clustering of diseases. J Autoimmun. 2009;33[3-4]: 197-207 doi: 10.1016/j.autrev.2011.11.012.

[15] Liu J, Wang C, Liu S. Recent Advances in the Diagnosis of Autoimmune Inner Ear Disease: A Scoping Review. Otolaryngology; 2025. Available from doi:10.1101/2025.01.22.25320943.

[16] Li X, Cao Z, Chen F, Yang D, Zhao F. Sensorineural hearing loss in autoimmune diseases: A systemic review and meta-analysis. J Int Adv Otol. 2023;19[4]:277-282

[17] Harris JP, Weisman MH, Derebery JM, *et al*. Treatment of corticosteroid-responsive autoimmune inner ear disease with methotrexate: A randomized controlled trial. JAMA 2003; 290:1875–83.

[18] Loveman DM, De Comarmond C, Cepero R, Baldwin DM. Autoimmune sensorineural hearing loss: clinical course and treatment outcome. Semin Arthritis Rheum. 2004;34[2]:538-543.

[19] Bovo R, Aimoni C, Martini A. Immune-mediated inner ear disease. Acta Otolaryngol. 2006;126[10]:1012-1021.

[20] Ciorba A, Corazzi V, Bianchini C, Aimoni C, Pelucchi S, Skarżyński PH, *et al*. Autoimmune inner ear disease (AIED): A diagnostic challenge. Int J Immunopathol Pharmacol. 2018 Jan;32:2058738418808680.

[21] Das S, Bakshi SS, Seepana R. Demystifying autoimmune inner ear disease. Eur Arch Otorhinolaryngol. 2019 Dec;276(12):3267–74.

[22] McCabe BF: Autoimmune inner ear disease: therapy. Am J Otol 1989, 10:196–197.

[23] Harris JP, Weisman MH, Derebery JM, *et al*.: Treatment of corticosteroid-responsive autoimmune inner ear disease with methotrexate: a randomized controlled trial. JAMA 2003, 290:1875–1883. An important paper, the first paper to emerge from the multicenter trial evaluating AIED.

[24] Bovo R, Ciorba A, Martini A. The diagnosis of autoimmune inner ear disease: evidence and critical pitfalls. Eur Arch Otorhinolaryngol. 2009 Jan; 266(1):37–40.

[25] McCabe BF: Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 88:585—589, 1979

[26] Hughes GB, Barna BP, Kinney SE, Calabrese LH, Nalepa NJ: Clinical diagnosis of immune inner ear disease. Laryngoscope 98:251—253, 1988

[27] Hughes GB, Kinney SE, Barna BP, Tomsak RL, Calabrese LH: Autoimmune reactivity in Cogan's syndrome: A preliminary report. Otolaryngol Head Neck Surg 91:24—32, 1983

[28] Moscicki RA, Ramadan H, Castro OJ, Nadol JB, Bloch KJ: Corticosteroid response and immunologic studies in idiopathic progressive sensorineural hearing loss. J Allergy Clin Immunol 81:217, 1988

[29] Hughes GB, Kinney SE, Barna BP, Calabrese LH: Practical versus theoretical management of autoimmune inner ear disease. Laryngoscope 94:758—766, 1984

[30] Summers RW, Harker L: Ulcerative colitis and sensorineural hearing loss: Is there a relationship? J Clin Gastroenterol 4:251-252, 1982

[31] Veldman JE: Immunology of hearing: Experiments of nature. Am J Otology 10:183—187, 1989

[32] Hughes GB, Barna BP, Kinney SE, Calabrese LH, Nalepa NL: Predictive value of laboratory tests in "autoimmune" inner ear disease: Preliminary report. Laryngoscope 96:502—505, 1986

[33] Arnold W, Pfaltz R: Critical evaluation of the immunofluorescence microscopic test for identification of serum antibodies against human inner ear tissue. Acta Otorhinolaryngol [Stockholm] 103:373—378, 1987

[34] McCabe BF: Autoimmune inner ear disease: Therapy. Am J Otology 10:196—197, 1989

[35] Lobo DR, García-Berrocal JR, Ramírez-Camacho R. New prospects in the diagnosis and treatment of immune-mediated inner ear disease. World J Methodol. 2014 Jun 26;4[2]:91-8. doi: 10.5662/wjm.v4.i2.91.

[36] Howick, J.; Chalmers, I.; Glasziou, P.; Greenhalgh, T.; Heneghan, C.; Liberati, A.; Moschetti, I.; Phillips, B.; Thornton, H. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine [OCEBM] Levels of Evidence [Background Document]. [2011]. 2018, Oxford Centre for Evidence-Based Medicine. Available online: https://www.cebm.ox.ac.uk/resources/levels-ofevidence/ocebm-levels-of-evidence [accessed on 21 July 2019].

[37] Gomaa, N.A.; Jimoh, Z.; Campbell, S.; Zenke, J.K.; Szczepek, A.J. Biomarkers for Inner Ear Disorders: Scoping Review on the Role of Biomarkers in Hearing and Balance Disorders. Diagnostics 2021, 11, 42. Diagnostics11010042

[38] Hajas, A.; Szodoray, P.; Barath, S.; Sipka, S.; Rezes, S.; Zeher, M.; Sziklai, I.; Szegedi, G.; Bodolay, E. Sensorineural hearing loss in patients with mixed connective tissue disease: Immunological markers and cytokine levels. J. Rheumatol. 2009, 36, 1930–1936. [CrossRef]

[39] Bovo, R.; Aimoni, C.; Martini, A. Immune-mediated inner ear disease. Acta Otolaryngol. 2006, 126, 1012–1021. [CrossRef]

[40] Maldonado, M.E.; Perez, M.; Pignac-Kobinger, J.; Marx, E.T.; Tozman, E.M.; Greidinger, E.L.; Hoffman, R.W. Clinical and immunologic manifestations of mixed connective tissue disease in a Miami population compared to a Midwestern US Caucasian population. J. Rheumatol. 2008, 35, 429–437.

[41] Greidinger, E.L.; Hoffman, R.W. Autoantibodies in the pathogenesis of mixed connective tissue disease. Rheum. Dis. Clin. 2005, 31, 437–450. [CrossRef] [PubMed]

[42] Alawieh, A.; Mondello, S.; Kobeissy, F.; Shibbani, K.; Bassim, M. Proteomics studies in inner ear disorders: Pathophysiology and biomarkers. Expert Rev. Proteom. 2015, 12, 185–196. [CrossRef] [PubMed]

[43] Chiarella, G.; Saccomanno, M.; Scumaci, D.; Gaspari, M.; Faniello, M.C.; Quaresima, B.; Di Domenico, M.; Ricciardi, C.; Petrolo, C.; Cassandro, C.; *et al*. Proteomics in Ménière disease. J. Cell. Physiol. 2012, 227, 308–312. [Cross Ref] [PubMed]

[44] Yukawa, K.; Hagiwara, A.; Ogawa, Y.; Nishiyama, N.; Shimizu, S.; Kawaguchi, S.; Nakamura, M.; Ito, H.; Tomiyama, S.; Suzuki, M. Bilateral progressive hearing loss and vestibular dysfunction with inner ear antibodies. Auris Nasus Larynx 2010, 37, 223–228. [CrossRef]

[45] Haase, G.M.; Prasad, K.N. Oxidative damage and inflammation biomarkers: Strategy in hearing disorders. Otol. Neurotol. 2016, 37, e303–e308. [CrossRef]

[46] Süslü, N.; Yilmaz, T.; Gürsel, B. Utility of anti-HSP 70, TNF-alpha, ESR, antinuclear antibody, and antiphospholipid antibodies in the diagnosis and treatment of sudden sensorineural hearing loss. Laryngoscope 2009, 119, 341–346. [CrossRef]

[47] Yehudai, D.; Shoenfeld, Y.; Toubi, E. The autoimmune characteristics of progressive or sudden sensorineural hearing loss. Autoimmunity 2006, 39, 153–158. [CrossRef]

[48] Betancur, J.F.; Londoño, A.; Estrada, V.E.; Puerta, S.L.; Osorno, S.M.; Loaiza, A.; Carmona, J.A.; Gómez-Puerta, J.A. Uncommon patterns of antinuclear antibodies recognizing mitotic spindle apparatus antigens and clinical associations. Medicine [Baltimore] 2018, 97, e11727. [CrossRef]

[49] Toubi, E.; Ben-David, J.; Kessel, A.; Halas, K.; Sabo, E.; Luntz, M. Immune-mediated disorders associated with idiopathic sudden sensorineural hearing loss. Ann. Otol. Rhinol. Laryngol. 2004, 113, 445–449. [CrossRef]

[50] Ikezono, T.; Matsumura, T.; Matsuda, H.; Shikaze, S.; Saitoh, S.; Shindo, S.; Hasegawa, S.; Oh, S.H.; Hagiwara, Y.; Ogawa, Y.; *et al*. The diagnostic performance of a novel ELISA for human CTP [cochlin-tomoprotein] to detect perilymph leakage. PLoS ONE 2018, 13, e0191498. [CrossRef]

[51] Calzada, A.P.; Lopez, I.A.; Beltran Parrazal, L.; Ishiyama, A.; Ishiyama, G. Cochlin expression in vestibular endorgans obtained from patients with Meniere's disease. Cell Tissue Res. 2012, 350, 373–384. [CrossRef]

[52] Pathak, S.; Hatam, L.J.; Bonagura, V.; Vambutas, A. Innate immune recognition of molds and homology to the inner ear protein, cochlin, in patients with autoimmune inner ear disease. J. Clin. Immunol. 2013, 33, 1204–1215. [CrossRef]

[53] Decourt, B.; Hillman, D.; Bouleau, Y.; Dulon, D.; Hafidi, A. Is otospiralin inner ear specific? Evidence for its expression in mouse brain. Int. J. Dev. Neurosci. 2009, 27, 87–96. [CrossRef]

[54] Robertson, N.G.; Resendes, B.L.; Lin, J.S.; Lee, C.; Aster, J.C.; Adams, J.C.; Morton, C.C. Inner ear localization of mRNA and protein products of COCH, mutated in the sensorineural deafness and vestibular disorder, DFNA9. Hum. Mol. Genet. 2001, 10, 2493–2500. [CrossRef] [PubMed]

[55] Schmitt, H.; Roemer, A.; Zeilinger, C.; Salcher, R.; Durisin, M.; Staecker, H.; Lenarz, T.; Warnecke, A. Heat Shock Proteins in Human Perilymph: Implications for Cochlear Implantation. Otol. Neurotol. 2018, 39, 37–44. [CrossRef]

[56] Jókay, I.; Papp, Z.; Soós, G.; Sziklai, I.; Dezsö, B. The effect of chronic otitis media on the immunoreactivity of the human inner ear. Eur. Arch. 2001, 258, 529–532. [CrossRef]

[57] Choi, S.H.; Choi, C.H. Noise-Induced Neural Degeneration and Therapeutic Effect of Antioxidant Drugs. J. Audiol. Otol. 2015, 19, 111–119. [CrossRef]

[58] Hoshino, T.; Tabuchi, K.; Nishimura, B.; Tanaka, S.; Nakayama, M.; Ishii, T.; Warabi, E.; Yanagawa, T.; Shimizu, R.; Yamamoto, M.; *et al*. Protective role of Nrf2 in age-related hearing loss and gentamicin ototoxicity. Biochem. Biophys. Res. Commun. 2011, 415, 94–98. [CrossRef]

[59] Kim, H.J.; So, H.S.; Lee, J.H.; Park, C.; Lee, J.B.; Youn, M.J.; Kim, S.J.; Yang, S.H.; Lee, K.M.; Kwon, K.B.; *et al*. Role of proinflammatory cytokines in cisplatin-induced vestibular hair cell damage. Head Neck J. Sci. Spec. Head Neck 2008, 30, 1445–1456. [CrossRef] [PubMed]

[60] Counter, S.A.; Buchanan, L.H. Neuro-ototoxicity in Andean adults with chronic lead and noise exposure. J. Occup. Environ. Med. 2002, 44, 30–38. [CrossRef]

[61] Deshpande, A.K.; Tan, L.; Lu, L.J.; Altaye, M.; Holland, S.K. fMRI as a Preimplant Objective Tool to Predict Postimplant Oral Language Outcomes in Children with Cochlear Implants. Ear Hear. 2016, 37, e263–e272. [CrossRef] [PubMed]

[62] Liu J, Wang C, Liu S. Recent Advances in the Diagnosis of Autoimmune Inner Ear Disease: A Scoping Review [Internet]. Otolaryngology; 2025 [cited 2025 Nov 4]. Available from: http://medrxiv.org/lookup/doi/10.1101/2025.01.22.25320943

[63] Rauch SD. Clinical management of immune-mediated inner-ear disease. Ann N Y Acad Sci. 1997;830:203-210.

[64] Breslin NK, Varadarajan VV, Sobel ES, Haberman RS. Autoimmune inner ear disease: A systematic review of management. Laryngoscope Investig Otolaryngol. 2020 Dec;5[6]:1217–26.

[65] Harris JP, Gopen Q, Kiethley E [2009] Autoimmune inner ear dis-ease and other autoimmune diseases with inner ear involvement. In: Snow JB, Wackym PA [eds]. Ballenger's otorhinolaryngology head and neck surgery, 17th edn. BC Decker Inc., Connecticut, pp 305–312

[66] Mijovic T [2013] Autoimmune sensorineural hearing loss: the otology-rheumatology interface. Rheumatology 52:780–789

[67] Das S, Bakshi SS, Seepana R. Demystifying autoimmune inner ear disease. Eur Arch Otorhinolaryngol. 2019 Dec;276[12]:3267–74.

[68] Sismanis A, Thompson T, Willis HE: Methotrexate therapy for autoimmune hearing loss: a preliminary report. Laryngoscope 1994, 104:932–934.

[69] Parnes LS, Sun AH, Freeman DJ: Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. Laryngoscope 1999, 109[7]:117.

[70] Sismanis A, Wise CM, Johnson GD: Methotrexate management of immune-mediated cochleovestibular disorders Otolaryngol Head Neck Surg 1997, 116:146–152.

[71] Luetje CM, Berliner KI: Plasmapheresis in autoimmune inner ear disease: long-term follow-up. Am J Otol 1997, 18[5]:572-6.