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Advances in immune mediated inner ear disease

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Immune-mediated inner ear disease (IMIED) is emerging in our understanding as a cause of sensorineural hearing loss (SNHL). It poses a considerable diagnostic challenge due to the lack of specific tests and diagnostic biomarkers as well as clinical features that overlap with other audiovestibular disorders. Cases may involve isolated inner ear dysfunction or occur in the context of systemic autoimmune diseases. IMIED pathogenesis involves the interplay of autoantibodies, cytotoxic T cells, and innate immune mechanisms. Corticosteroid responsiveness is a defining feature of IMIED, but refractory cases may require alternative immunosuppressive agents. Although emerging immunosuppressive regimens demonstrate potential efficacy, larger trials are warranted to establish diagnostic and therapeutic guidelines. While symptomatic treatments including hearing aids and cochlear implants are beneficial in patients with IMIED associated hearing loss, future strategies focus on preventing irreversible inner ear damage and preserving hearing by developing innovative immunomodulatory strategies.

KEYWORDS

hearing loss, immunity, macrophages, autoimmunity, inner ear

1 Introduction

Traditionally, the pathological mechanisms underpinning many audiovestibular conditions have remained largely unknown and diagnosis has been made purely on symptomatic features. However, serological biomarkers have linked some of these symptoms to systemic or localized autoimmune conditions. Research has also shed light on the role the inner ear immune system plays in maintaining homeostasis and response to injury and pathogens (Keithley, 2022). Interestingly, while the normal immune response in the inner ear can sometimes cause damage, there are cases where individuals experience either an exaggerated immune response, that can cause more damage compared to their normal peers, or have an abnormal immune response and suffer damage in situations where their normal peers would not. The latter category includes patients that have immune systems that fail to recognize self-antigens resulting in autoimmunity. The field is now being redefined as a spectrum of immune mediated inner ear disease (IMIED) that encompasses a normal response, to an abnormal response to an autoimmune response. In this review we discuss the implications for diagnosis and management of the abnormal and autoimmune response in the inner ear.

2 Definition

Autoimmune inner ear disease (AIED) is classically defined based on a presentation of progressive or fluctuating bilateral hearing loss with or without vestibular dysfunction secondary to an uncontrolled immune system response, typified by the loss of

immunological tolerance to self-antigens (Ciorba et al., 2018). This classical definition is useful in alerting the treating clinician as to when an autoimmune cause should be suspected but relies on identifying the uncontrolled immune response in terms of positive serum biomarkers. Given the lack of validated biomarkers for AIED coupled with the difficulties of inner ear tissue sampling, the diagnosis is restricted to a limited population. It ignores the practicality that many patients can potentially benefit from treatment with immunomodulatory agents. With new knowledge of the immune function in the inner ear it is now time to redefine and expand the definition of AIED to encompass IMIED.

IMIED is sensorineural hearing loss or peripheral vestibular dysfunction, where there is an aberrant response by a component of the patient's own immune system resulting in inner ear dysfunction. It is important to note that this definition does not include the many inner ear conditions that have an immune basis for their pathogenesis but rather those patients that have abnormalities in their immune system that cause them to have disease when other "normal" patients do not. Diseases like vestibular schwannoma, chronic suppurative otitis media and noise induced hearing loss have immune responses that contribute to inner ear dysfunction; however, this is likely the normal response to insult (Sagers et al., 2019; Sai et al., 2022; Xia et al., 2022).

IMIED encompasses conditions that we are now recognizing as occurring in the ear, where overactive immune cells are causing injury through classical autoimmune mechanisms but additionally also cause disease through mechanisms outside the typical loss of self-tolerance and the failure to distinguish between self and non-self-antigens. Accordingly, we now know that immune disease can present in the ear as non-progressive and non-fluctuating symptoms which is outside the traditional clinical definition of AIED. Patients presenting only with inner ear disease are typically classified as primary AIED, whereas those where inner ear disease that occurs in the context of systemic autoimmune disease are classified as secondary AIED (Aftab et al., 2010). This again is an oversimplification that suggests either only the ear or the whole body is affected by the autoimmune condition, when in reality, primary AIED patients likely have manifestations that may have gone undetected or have led to generalized conditions that have not been recognized as autoimmune. Examples include skin rashes, arthritis, diabetes, and vascular disease. For the purposes of this review, many of the discussion points will change between AEID and IMIED reflecting the blurred lines between these old and new definitions. The novel IMIED definition presented here represents a more pragmatic definition in that it suggests whether an inner ear condition should be treated with immunomodulators or not.

3 Historical perspective

The field of immunology has its origins in the late nineteenth century with the discovery by Metchnikff of phagocytic cells, that later became known to have a central role in the innate immune system. Subsequently, Behrig and Ehrlich's discovery of antibodies established the basis for adaptive immunity. The concept of autoimmunity emerged in 1938 following Dameshak and Schwartz's work on hemolytic anemia (Ahsan, 2023).

In 1958, Lehnhardt was the first to propose that anti-cochlear antibodies could explain bilateral hearing loss in patients with delayed hearing loss in the contralateral ear (Lehnhardt, 1958). Later, in 1979, McCabe documented a series of 18 patients with progressive bilateral hearing loss. After ruling out infectious and neoplastic causes, hearing improvements were demonstrated with an immunomodulatory treatment using corticosteroids and cyclophosphamide (McCabe, 1979).

The inner ear was once thought to be an "immune-privileged" site largely due to the tight junctions of the stria vascularis that form the blood-labyrinth barrier (BLB) (Harris, 1984, 1983). It was suggested that if this barrier was compromised and inner ear antigens were released, the immune system would treat them as foreign (Harris et al., 1985). However, later research revealed that the inner ear can actively process antigens, release cytokines, and recruit immune cells from the systemic circulation (Harris et al., 1997).

Harris and Sharp further demonstrated antibodies against inner ear antigens in the serum of patients with progressive sensorineural hearing loss suggesting that these antibodies may be mechanistically linked to hearing loss (Harris and Sharp, 1990). This was followed by confirmation that the presence of a circulating antibody to a 68 KDa component of a bovine inner ear extract correlates with progression of hearing loss and response to corticosteroid in patients with idiopathic, progressive, bilateral sensorineural hearing loss. The 68 kDa protein was subsequently identified as heat shock protein 70 (HSP-70), which is widely expressed in human tissues, including the inner ear, further supporting a pathogenic role for these antibodies in hearing loss (Moscicki et al., 1994). These seminal studies established AIED, and the broader concept of IMIED, as a potentially treatable cause of sensorineural hearing loss that could be defined by both functional and potentially biochemical biomarkers.

4 Epidemiology

Estimating the true prevalence of IMIED is challenging due to the absence of definitive diagnostic tests or imaging and its clinical presentation that overlaps with other audiovestibular disorders. Currently, the prevalence of AIED, based on its classical definition, is estimated at 15 cases per 100,000 people, translating to ~45,000 cases annually in the United States. AIED is reported to be more common in women between in their third to sixth decade (Ciorba et al., 2018). This estimate is based on the incidence of AIED being significantly lower than the rate of sudden SNHL, that occurs at a rate of 5–20 cases per 100,000 per year (George and Pradhan, 2009). The progression from initial symptoms to treatment-resistant disease, requiring rehabilitative strategies such as hearing aids, typically takes about 3 years. With a U.S. population of 300 million, the point prevalence of AIED is estimated at around 45,000 individuals (Vambutas and Pathak, 2016). However, the actual incidence and prevalence of IMIED, if redefined as proposed here, are likely much higher. This discrepancy highlights the need for improved diagnostics and broader recognition of IMIED within the Otolaryngology and Primary Care communities.

In the United States, it is estimated that 15–20 million people have immune-mediated diseases, and individuals with IMIED are

likely a significant, underrecognized subset of this group (Roberts and Erdei, 2020). The actual prevalence may be even higher, as many cases of progressive hearing loss or vestibular dysfunction currently labeled as idiopathic or hereditary may have an immune-related origin. IMIED can therefore be categorized into two groups: secondary cases, where a systemic immune disease or specific trigger is documented, and primary cases, where no systemic immune condition, symptoms, or clear trigger is identified. Most patients fall into the primary category, which aligns with the classical definition of AIED. This underscores the substantial work needed to better understand and address these conditions (Harris and Weisman, 2007).

5 The inner ear immune system, autoimmunity and immune mediated injury

Autoimmunity refers to the immune system's coordinated response against the body's own healthy cells and tissues. While self-reactive antibodies and T cells are naturally present in all healthy individuals, autoimmune disease occurs when this self-recognition becomes pathological and leads to immune attacks against the body's own tissues. This happens due to a breakdown in immunological tolerance, where self-antigens are no longer ignored by the immune system. The causes of autoimmunity are complex and involve a combination of genetic, environmental, and hormonal factors. Autoimmune diseases vary widely in severity, ranging from asymptomatic biochemical abnormalities to severe organ failure, and can be categorized as either organ-specific or systemic (Pisetsky, 2023).

At its core, autoimmunity arises from an overactive immune system, triggered by the loss of self-tolerance, leading to cellular damage in ways that would not occur without the underlying trigger. Advances in whole genome sequencing and genome-wide association studies (GWAS) are shedding light on the genetic factors contributing to these diseases (Hocking and Buckner, 2022). For instance, a gain-of-function mutation in *TLR7* has been linked to increased activation of TLR7 and B cells, resulting in childhood-onset systemic lupus erythematosus (SLE). However, many common autoimmune diseases are polygenic, involving multiple genetic factors (Brown et al., 2022; Grimbacher et al., 2016).

The inner ear is isolated from the systemic circulation by the BLB, which is characterized by non-fenestrated capillaries with tight junctions. This anatomical barrier ensures the separation of cochlear and vestibular tissues and fluids from the rest of the circulatory system (Nyberg et al., 2019). However, the inner ear interacts with the systemic immune system via the circulation and lymph to respond to homeostatic perturbations, including noise trauma and infection (Keithley, 2022).

The immune system of the inner ear comprises both innate and adaptive components. Following noise-induced trauma or middle ear infections, studies have shown that elements of these systems, including T cells, B cells, natural killer (NK) cells, macrophages, and neutrophils, are actively recruited to the cochlea (Rai et al., 2020). A key aspect of the inner ear's innate immunity is the presence of resident macrophages, which originate from the yolk sac and fetal liver. These macrophages maintain their population through self-renewal and the infiltration of circulating monocytes (Hough et al., 2022; Kishimoto et al., 2019; Miwa and Okano, 2022; Hu et al., 2018; Francis and Cunningham, 2017). These inner ear macrophages include the "cochlear macrophages" in the spiral ligament and the "perivascular macrophage-like melanocytes" in the stria vascularis (Zhang et al., 2012). The stria vascularis therefore acts as important interface between inner ear structures and the immune system and is also an important site of cytokine signaling within the inner ear (Samaha et al., 2021).

Cochlear macrophages have diverse roles including phagocytosis, antigen presentation and cytokine secretion (Liu and Xu, 2024). Similar to macrophages in other organs, cochlear macrophages can be broadly classified into M1 and M2 subtypes. M1-polarized macrophages are pro-inflammatory, secreting interleukin-12 (IL-12) and tumor necrosis factor-alpha (TNF-α) to promote inflammation and recruit additional immune cells. In contrast, M2-polarized macrophages secrete interleukin-4 (IL-4) and interleukin-10 (IL-10) and are primarily involved in wound healing and tissue repair (Miwa and Okano, 2022). The M1/M2 dichotomy is however likely to be an over simplification, and it has been demonstrated that cochlear macrophages are predominantly multi-marker M1/M2 mixed lineage macrophages (Bedeir et al., 2022). It is known that inhibition of pro-inflammatory M1 macrophages or induction of M2 macrophages results in attenuated experimentally induced inflammatory bowel disease (Zhu et al., 2016). It is thus speculated that similar class switching may be an important mechanism of IMIED (Miwa and Okano, 2022). There is evidence that cochlear trauma activates resident cochlear macrophages, switching them to a pro-inflammatory M1 state and in turn stimulating the recruitment other immune cells into the cochlea (Frye et al., 2017). A major component of the inner ear immune response, for example to noise trauma, is the secretion of tumor necrosis factor (TNF-α), interleukin 1β (IL-1β) and IL-6 thought to be by cochlear macrophages (Landegger et al., 2019). There is therefore increasing evidence that macrophages are important effectors of cochlear damage via their pro-inflammatory and fibrogenic functions (Navegantes et al., 2017).

Evidence suggests that resident cochlear macrophages also have a neuroprotective role, migrating to the synaptic region of inner hair cells in response to noise-induced synaptopathy. These macrophages are both essential and sufficient for restoring synaptic function following noise exposure (Manickam et al., 2023). It is therefore likely cochlear macrophages play multiple context dependent roles within the cochlea and can ultimately be both protective and detrimental to cochlear function.

Neutrophils play a critical role in the immune response to chronic suppurative otitis media (CSOM) (Khomtchouk et al., 2021). Two-photon intravital microscopy has shown that, following intracochlear lipopolysaccharide inoculation in mice, neutrophils are recruited to the cochlea via ICAM-1 expression in the spiral ligament (Bae et al., 2021). However, despite the well-established link between CSOM and sensorineural hearing loss (SNHL), it is macrophages rather than neutrophils that mediate inner ear damage. In a validated *Pseudomonas aeruginosa* CSOM mouse

model, macrophage infiltration of the cochlea was found to correlate with outer hair cell loss. This suggests that monocyte-to-macrophage differentiation within the cochlea is a key driver of immune-mediated damage (Xia et al., 2022).

Lymphocytes have also been detected in surgically obtained human cochleae, and evidence of T-lymphocyte/macrophage interactions supports the hypothesis that antigen-presenting activity occurs within the inner ear (Liu and Rask-Andersen, 2019). In mouse models, lymphocyte populations increase 4–7 days after noise exposure, neutrophils peak at 1 day, and myeloid cells reach their maximum levels after 14 days (Rai et al., 2020). It has also been proposed that interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) upregulate ICAM-1 expression on the spiral modiolar vein, facilitating the recruitment of systemic immune cells into the inner ear (Suzuki and Harris, 1995).

The endolymphatic sac (ES) plays a dual role in maintaining inner ear fluid homeostasis and contributing to innate immunity through the expression of genes such as *TLR4*, *TLR7*, beta-defensin, and lactoferrin. Research indicates that the ES serves as the primary antigen-processing site of the inner ear and acts as its primary immunological defense organ (Kämpfe Nordström et al., 2019). The ES also houses various immune cells, including macrophages, monocytes, and lymphocytes, specifically T cells and B cells containing IgG, IgM, and IgA (Keithley, 2022). However to date, the precise spatiotemporal coordination of the inner ear's immune response remains incompletely understood.

5.1 Pathophysiology of IMIED

The pathophysiology of IMIED remains poorly understood due to the lack of histological samples from living patients. Much of the current knowledge is derived from animal models, including genetically modified mice, rats, and guinea pigs (Goodall and Siddiq, 2015). IMIED can generally be classified as either cell-mediated, involving mature T cells, macrophages, and neutrophils, or humoral, driven by antigen-specific antibodies produced by B cells.

Cell-mediated IMIED has been modeled in rats by inducing labyrinthitis through the transfer of autoreactive T cells, which led to inflammation in naïve recipients (Gloddek et al., 1997). Additional studies using radiolabeled lymphocytes demonstrated their migration to the inner ear in response to antigenic stimuli mediated by ICAM-1 expression (Gloddek et al., 1991). Humoral mechanisms have been explored by sensitizing guinea pigs with Keyhole Limpet Hemocyanin (KLH), resulting in anti-KLH antibodies that correlated with hair cell and supporting cell damage in the inner ear (Harris, 1983). It is therefore evident that both cell mediated and humoral mechanisms are likely important in the pathophysiology of IMIED. However, although these models are useful as mechanistic descriptions, they were unable to be used to design therapeutic interventions, as a similar efficacy of immunomodulation, by protecting against hearing loss with etanercept treatment, was not achieved in humans with AIED (Wang et al., 2018; Cohen et al., 2005).

Like other autoimmune conditions, AIED occurs in part as a result of a loss of self-tolerance with the development of proinflammatory T cell and autoantibody production. Tolerance is defined as the prevention of an immune response against a defined antigen, for example self-antigens. Immune tolerance is maintained by a number of mechanisms including the elimination or suppression of autoreactive cells, regulatory immune cells and the maintenance of immune privileged sites such as the eye and brain (Sykes, 2007). Failures in these mechanisms can result in autoimmunity. Although thousands of cochlear proteins have been identified, including 4,435 in a quantitative proteomic study of the mouse cochlea (Miao et al., 2021), the specific inner ear antigens implicated in AIED remain largely unknown.

Some studies have suggested that IgG antibodies target inner ear proteins like cochlin, β-tectorin, and HSP-70 in patients with idiopathic sensorineural hearing loss (Tebo et al., 2006). This points to a potential Type II hypersensitivity reaction involving complement activation, antibody-dependent cellular cytotoxicity, or anti-receptor activity (Warrington et al., 2011). However, the pathogenic role of these autoantibodies, particularly HSP-70, remains unclear (Yeom et al., 2003).

Additional postulated mechanisms of inner ear cellular damage in IMIED include the direct activation of the complement system, action of cytotoxic T cells (type IV response) whereby T cells can cause cell lysis via the release of cytotoxins and additionally release proinflammatory cytokines TNF-α and IFN-γ leading to the recruitment and activation of macrophages and immune complex deposition (type III immune response) which cause a vasculitis of inner ear vessels resulting in cochlear and vestibular damage especially if the labyrinthine artery, the major blood supply of the inner ear, is affected. Ultimately, these processes lead to audiovestibular dysfunction via several mechanisms, including hair cell and supporting cell apoptosis, increased vascular permeability, loss of the blood labyrinthine barrier with potential subsequent exposure of the inner ear to environmental toxins, and the disruption of electrochemical gradients by damage to the stria vascularis (Goodall and Siddiq, 2015). Histological findings from mouse models and human temporal bones with AIED have revealed cochlear vasculitis, otospongiosis, endolymphatic hydrops, and degeneration of the Organ of Corti and spiral ganglion neurons (Schwartz et al., 1992; Kamakura et al., 2017).

The triggers for autoimmunity in IMIED remain speculative but may involve molecular mimicry from viral or bacterial infections and exposure to pathogen-associated molecular patterns (PAMPs), including endotoxin or lipopolysaccharide, activate both innate and adaptive immune responses (Cusick et al., 2012; Gauthier et al., 2022) (Figure 1).

Genetic predispositions also play a role in IMIED. Variants in immune-related genes have been linked to autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, suggesting similar mechanisms may underlie IMIED (Lenz et al., 2015). Specific HLA haplotypes, including HLA-B27, B35, and A1-B8-DR3, have been associated with AIED (Psillas et al., 2021, 2022). Environmental factors, such as female sex hormones, smoking, microbiome dysbiosis, and vitamin deficiencies, may also modulate susceptibility to IMIED (Nusbaum et al., 2020; Pisetsky, 2023). However, these triggers remain challenging to define given the diversity of potential insults the inner ear encounters over a lifetime (Touil et al., 2023).

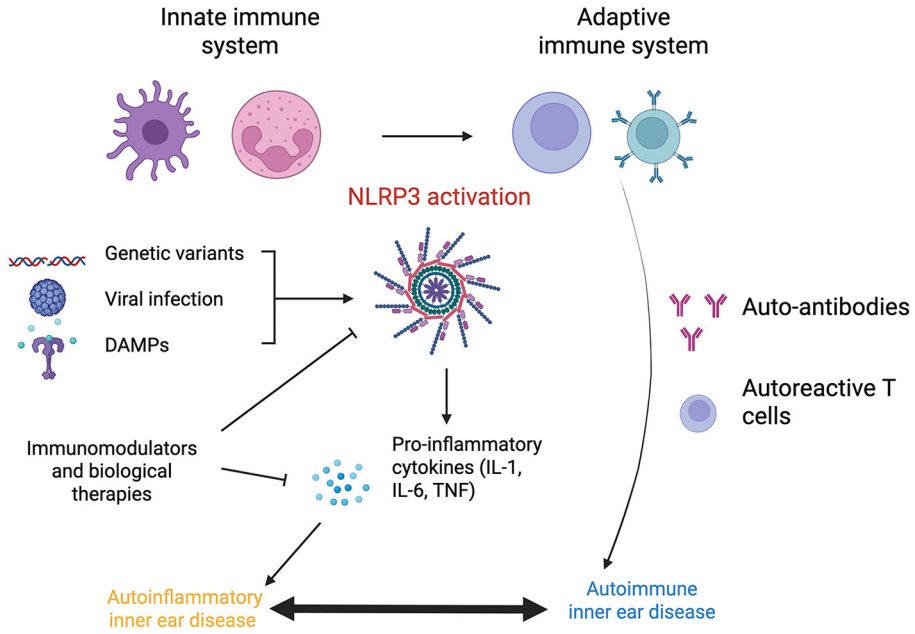

FIGURE 1
Innate and adaptive immune responses in IMIED.

5.2 Types of immune mediated inner ear diseases

AIED, characterized by a loss of self-tolerance, can present as an isolated condition in ~70% of cases, where the inner ear is exclusively affected, or as part of a systemic autoimmune disorder (Table 1). While some pathophysiological mechanisms of AIED have been elucidated, the underlying etiology of primary inner ear immune conditions remains largely unknown, apart from their association with the described HLA haplotypes. It is plausible that other, yet unidentified, genetic or epigenetic factors contribute to the development of AIED. The application of next-generation sequencing technologies offers hope for identifying these candidates in the future (Wajda et al., 2021).

Emerging research indicates that IMIED, where self-tolerance is preserved but the immune system exhibits hyperactivity or a gain-of-function response, may also be implicated in inner ear pathology. The inner ear immune system reacts to disruptions in cochlear homeostasis, such as those caused by noise or infection, by initiating an immune response (Liu and Xu, 2024). It is likely that IMIED arises from environmental triggers, which may remain undefined, interacting with a genetically susceptible background. Conversely, in individuals with a non-permissive genetic background, the same environmental triggers might elicit a controlled immune response that does not harm the host.

5.2.1 Autoinflammatory hearing loss

An overactive or injurious immune-mediated inflammatory response has been identified as a potential common pathway for hearing loss associated with various conditions, including noise exposure, aging, tumors, chronic suppurative otitis media, and auto-inflammatory diseases (Sagers et al., 2019; Xia et al., 2022). Autoinflammatory hearing loss, characterized by dysregulation of the innate immune system, is driven by monocyte activation and does not require specific antibody or T cell responses (Nakanishi et al., 2020).

A central player in autoinflammatory diseases is the NLRP3 inflammasome, a key effector in cellular inflammation. The NLRP3 inflammasome consists of the cytosolic pattern recognition receptor NLR family pyrin domain containing 3, caspase-1, and an apoptosis-associated speck-like protein containing a CARD (ASC). It is increasingly recognized as a potential mechanism for hearing loss in various disease states (Gregory et al., 2023). Activation of the NLRP3 inflammasome in cochlear macrophages, triggered by a wide range of danger signals, has been shown to be a key driver in hearing loss associated with CSOM (Schiel et al., 2024).

NLRP3 activation leads to the oligomerization of ASC and the activation of caspase-1. This process results in the maturation of the pro-inflammatory cytokines pro-IL-1β and pro-IL-18, converting them into their active forms. Caspase-1 also facilitates the formation of pores in the plasma membrane, enabling the secretion of IL-1β and IL-18, which can induce pyroptosis, a form of inflammatory cell death. The TNF and IL-1 pathways converge on c-Jun N-terminal kinase (JNK), a downstream effector that controls cellular functions, including survival and apoptosis (Dhanasekaran and Reddy, 2017) (Figures 2, 3).

Mutations activating the NLRP3 inflammasome are known to cause a spectrum of autoinflammatory diseases called cryopyrin-associated periodic syndromes (CAPS), which include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease. These conditions are characterized by IL-1β mediated inflammation

TABLE 1 Summary of systemic autoimmune diseases that have been reported to be associated with audiovestibular dysfunction with the prevalence of audiovestibular symptoms and relevant biomarkers.

Autoimmune disease	Prevalence of audiovestibular involvement	Clinical features	Biomarkers
Systemic lupus erythematosus	6–70%	Multiorgan involvement including skin, neurologic system, musculoskeletal system. SNHL, tinnitus, vertigo.	ANA, anti dsDNA, anti-SSA/Ro, Anti Smith, antiphospholipid
Cogan syndrome	31–45%	Eye involvement—interstitial keratitis. Systemic—arthralgia, fever, aortitis SNHL, vestibular deficits	Anti-HSP70, ANCA, RF, ANA, anticardiolipin
Sarcoidosis	5–96%	Multisystemic granulomatous disease SNHL	ACE levels, SAA, sIL-2R, ESR
Rheumatoid arthritis	25–72%	Systemic autoimmune disease with intra-articular and extra-articular features. SNHL	RF, anti-CCP, ESR
Antiphospholipid syndrome	Case reports only	Systemic autoimmune disease causing hypercoagulability. SNHL and sudden sensorineural hearing loss.	aCL, anti-beta-2-glycoprotein I, lupus anticoagulants
Polyarteritis nodosa	Case reports only	Autoimmune vasculitis. Middle ear effusions, SNHL.	No specific biomarkers, ESR/CRP
Behcet's disease	12–80%	Autoimmune vasculitis, SNHL	No specific biomarkers, ESR/CRP
Takayasu's arteritis	Case reports only	Autoimmune vasculitis, SNHL	No specific biomarkers, ESR/CRP
Relapsing polychondritis	40–54%	Autoimmune connective tissue disease, SNHL	No specific biomarkers, ESR/CRP
Granulomatosis with polyangiitis	8–65%	Autoimmune vasculitis, SNHL	c-ANCA, ESR, creatinine levels
Susac syndrome	Case reports only	Autoimmune vasculitis, SNHL	AECAs
Myasthenia gravis	22–34%	Autoimmune disease affecting neuromuscular junction, SNHL	Anti-MuSK, AChR
Multiple sclerosis	1–28%	Autoimmune inflammatory demyelinating disease, SNHL	No specific biomarkers
Hashimoto thyroiditis	Case reports only	Autoimmune thyroid disease, SNHL	TPOAb
Mixed cryoglobulinaemia	22%	Autoimmune vasculitis, SNHL	Cryoglobulin levels
Giant cell arteritis	7–100%	Autoimmune vasculitis	No specific biomarkers, ESR/CRP
Vogt-Koyanagi-Harada's disease	48–62%	Systemic granulomatous disease, SNHL	No specific biomarkers
Ulcerative colitis	2–5%	Autoimmune inflammatory bowel disease, SNHL	CBC, ESR, CRP, no specific biomarker

Adapted from Ralli et al. (2018). SNHL, Sensorineural hearing loss; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, anti-nuclear antigen; anti-dsDNA, anti-double stranded, DNA; ANCA, antineutrophil cytoplasmic antibodies; RF, rheumatoid factor; Anti-MuSK, anti muscle specific kinase; anti-AChR, anti-acetylcholine receptor; TPOAb, thyroid peroxidase antibody; ACE, angiotensin converting enzyme; SAA, serum amyloid A; sIL-2R, soluble interleukin 2 receptor; aCL, anti-cardiolipin.

affecting the skin, joints, eyes, and central nervous system, often with hearing loss (Nakanishi et al., 2020). A mutation in NLRP3 has also been implicated in non-syndromic hearing loss, specifically DFNA34, with some evidence showing that hearing loss can be reversed or reduced with anakinra treatment (Nakanishi et al., 2017). In a recent case at our institution, a patient with bilateral fluctuating hearing loss and no formal systemic immune diagnosis was found to carry a variant in *NOD2*, a gene associated with Crohn's disease and Blau syndrome and a known inhibitor of the NLRP3 inflammasome (Mao et al., 2022). Subsequent treatment with anakinra resulted in stabilization of the patient's hearing.

Given the growing evidence of the NLRP3 pathway's role in inflammation and hearing loss, there is increasing clinical interest in developing NLRP3 inhibitors. These inhibitors are likely to play an increasingly important role in managing IMIED in the future (El-Sharkawy et al., 2020; Vande Walle and Lamkanfi, 2024).

6 Clinical presentation and diagnosis of IMIED

AIED has classically been described as presenting with bilateral sensorineural hearing loss and has been separated from sudden sensorineural hearing loss as developing more slowly, with an onset over 3 to 90 days (Bovo et al., 2009). However, this distinction is outdated, as both autoimmune conditions and IMIED can manifest as sudden hearing loss, while non-immune conditions may evolve over longer periods. IMIED should therefore be considered in patients with sudden, rapidly progressive, or fluctuating sensorineural hearing loss, particularly when there is a response to steroids or signs of immune involvement in other organ systems.

AIED often begins unilaterally and progresses to bilateral hearing loss in 80% of cases. The progression tends to be

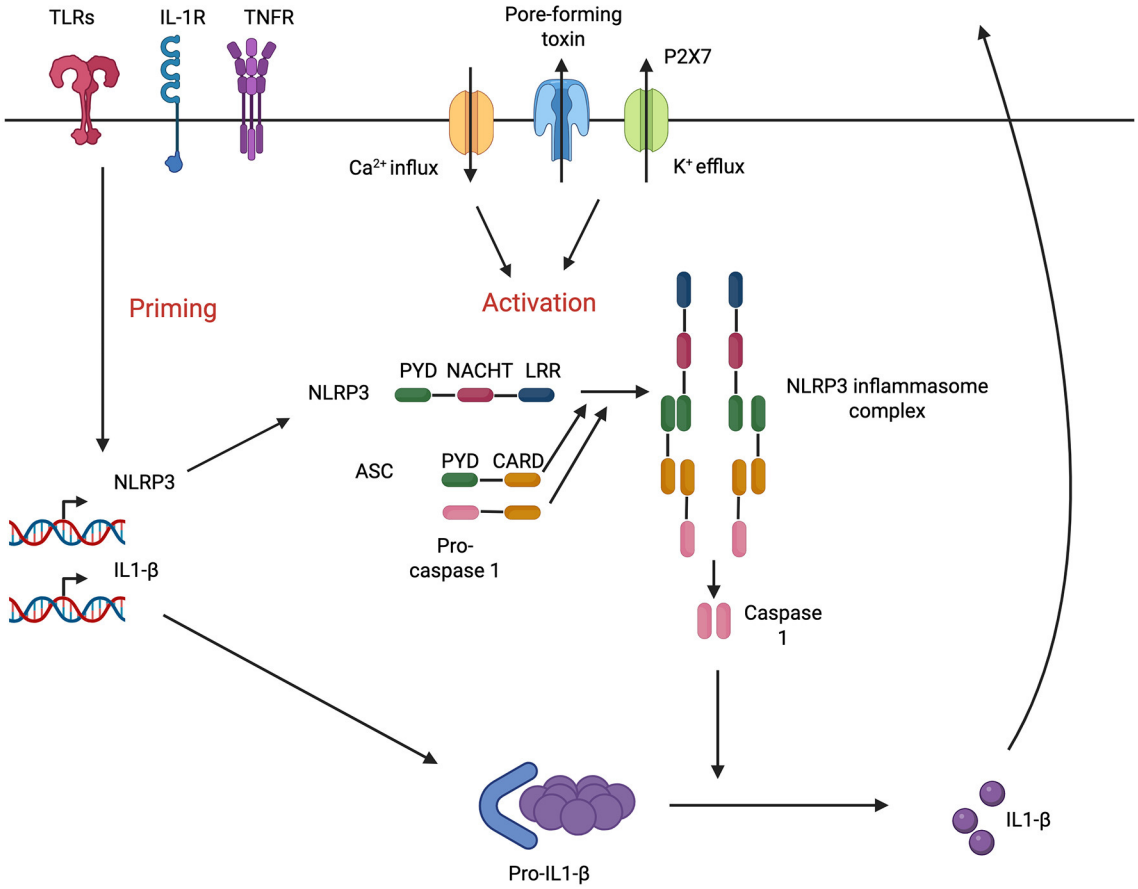

FIGURE 2
NLRP3 pathway in cochlear macrophages. Adapted from Nakanishi et al. (2017).

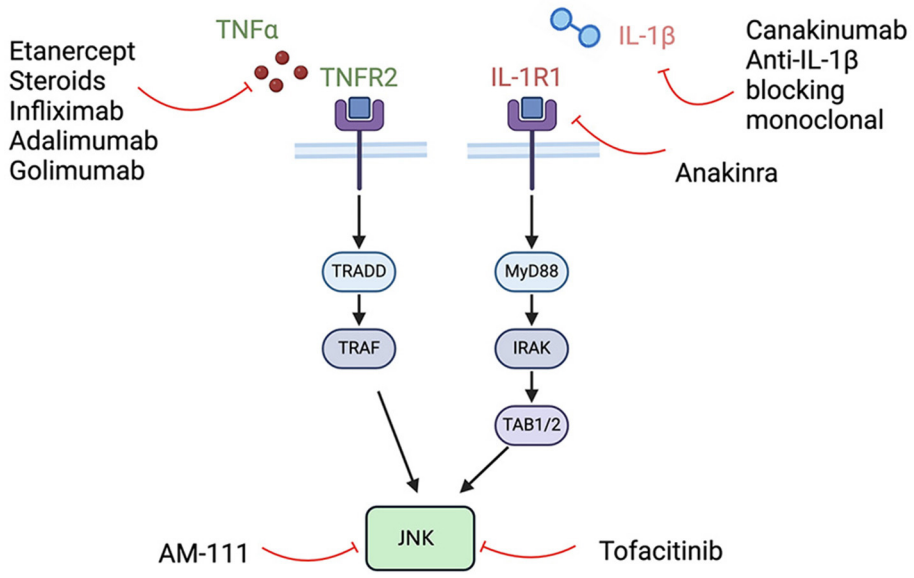

FIGURE 3
TNF alpha and IL1β pathways and drug inhibitors used in the treatment of IMIED.

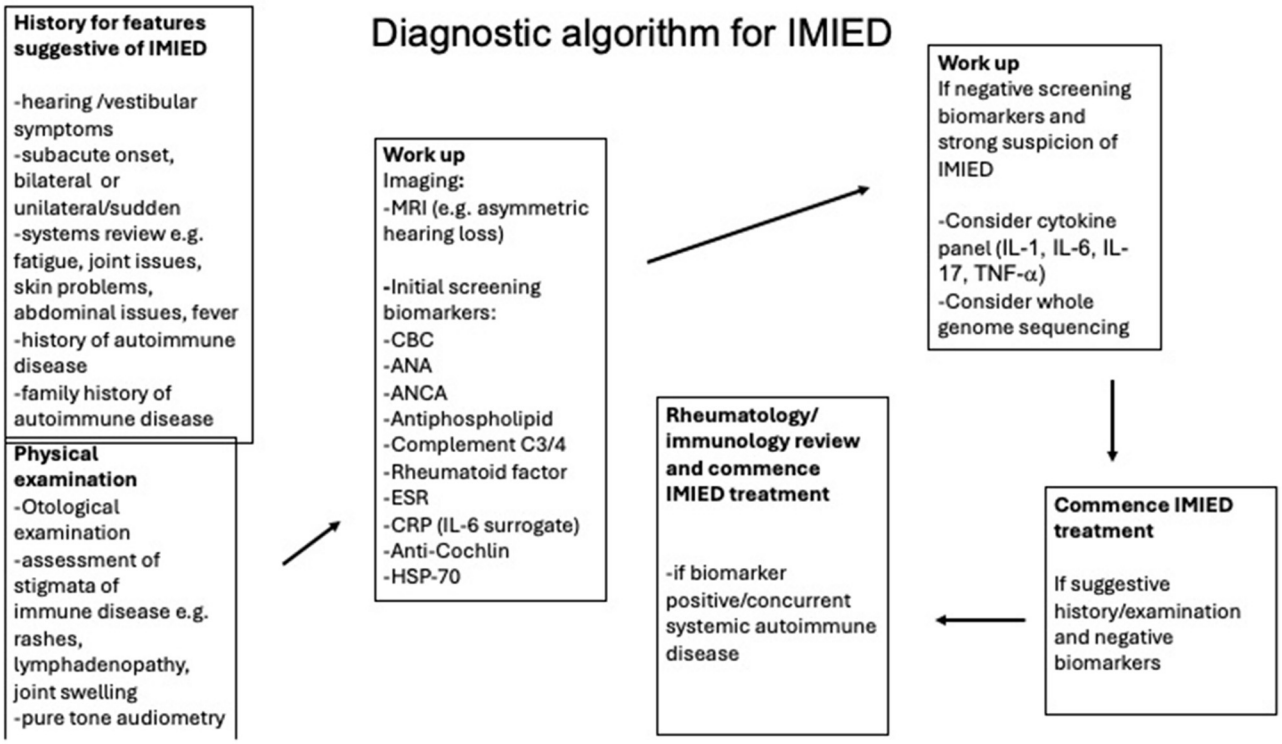

FIGURE 4
Proposed diagnostic algorithm for IMIED.

non-linear, with fluctuating hearing levels, though some patients may experience non-progressive hearing loss. Vestibular symptoms such as vertigo and disequilibrium are common, affecting ~50% of patients. These may be accompanied by horizontal-torsional nystagmus, reflecting asymmetric vestibular input characteristic of peripheral vestibulopathy. Early in the disease, vestibular signs may be intermittent, but over time, progressive involvement can lead to bilateral vestibular loss and the absence of nystagmus due to symmetric dysfunction (Mijovic et al., 2013). Additional otological symptoms include aural fullness and tinnitus. In the early stages of IMIED, when hearing fluctuations coincide with aural pressure and tinnitus, a differential diagnosis of Meniere's disease should be considered. It is possible that a subset of Meniere's patients have an underlying immune etiology. Studies have shown that some Meniere's patients have elevated levels of autoantibodies or circulating immune complexes against inner ear antigens, and epidemiological data suggest a higher prevalence of concurrent autoimmune conditions in this population (Lopez-Escamez et al., 2023; Kim et al., 2014).

Ultimately, it is crucial for clinicians to recognize the clinical features of IMIED, which should prompt further investigation of the immune system and the initiation of immunomodulatory therapies. We recommend considering any newly diagnosed sudden sensorineural hearing loss (SNHL) or vestibular dysfunction that improves with immunomodulation as a possible case of IMIED, with their future response to steroid treatment either confirming or excluding the diagnosis. While a personal or family history of autoimmune disease strengthens the diagnosis, it is not an absolute requirement for diagnosis.

6.1 Diagnosis and work up of IMIED

A proposed diagnostic algorithm for immune-mediated inner ear disease (IMIED) is shown in Figure 4, although it is important to note that no definitive biomarker, audiological test, or imaging modality currently exists for diagnosing IMIED. As a result, the diagnosis is based on the clinical history and the patient's response to immunosuppression. The classic definition of AIED involves idiopathic, progressive, bilateral sensorineural hearing loss of 30 dB or more at one or more frequencies (ranging from 250 to 8,000 Hz), with deterioration in at least one ear within the last 3 months. This deterioration is typically defined by a threshold shift of ≥15 dB at one frequency, 10 dB at two or more consecutive frequencies, or a significant change in speech discrimination scores (Moscicki et al., 1994). Additionally, a demonstrable improvement in hearing after systemic steroids is often considered a key diagnostic criterion (Matsuoka and Harris, 2013). However, if applied strictly, this legacy definition may lead to underdiagnosis and the failure to treat many patients who would benefit from immunomodulatory therapy.

Ultimately, IMIED is believed to have an underlying immune cause (which may not always be identifiable) and typically involves hearing loss or vestibular dysfunction that can be reversed

or improved with immunomodulation in the short term. The pattern of hearing loss can vary significantly, with different tonal frequencies affected, and can involve high, mid, or low tones, or even lead to more significant speech discrimination issues. Tympanometry results are usually normal unless middle ear disease is present, which may be associated with systemic immune conditions.

In cases where central pathology is suspected, gadolinium-enhanced MRI may be used for exclusion. Vestibular testing can help identify underlying dysfunction, revealing potential abnormalities in caloric testing, video head impulse test (vHIT), and cervical vestibular evoked myogenic potentials (cVEMPs) (Mendis et al., 2022).

Our recommended standard workup for suspected IMIED includes serological testing, including:

- Full blood count with differential
- Antinuclear antibody (ANA)
- Antineutrophil cytoplasmic antibodies (ANCA)
- Antiphospholipids
- Rheumatoid factor (RF)
- Complement C3/C4
- Anti-cochlin, anti-HSP70 antibodies
- Erythrocyte sedimentation rate

However, the role of these biomarkers remains controversial due to their low diagnostic value for both inner ear and immune-related conditions. For example, the HSP70 antibody was initially thought to correlate with steroid responsiveness, but later studies revealed it was present in a wide range of disease states, including in healthy individuals (Tebo et al., 2006). Similarly, the creation of anti-HSP70 antibodies in mouse models did not lead to hearing loss (Trune et al., 1998), though anti-HSP70 antibodies might still be useful for diagnosing Cogan's syndrome (Bonaguri et al., 2014).

A cytokine panel may also be ordered to check for elevated IL-1, IL-6, IL-17, and TNF-α levels in the peripheral blood, although these cytokine profiles do not currently correlate with changes in the inner ear (Quan et al., 2021). The cytokine profile might, however, guide therapeutic decisions. For example, a patient in our clinic with fluctuating hearing loss was found to have low serum IL-2R levels, which prompted a trial of anti-TNFα therapy. Low IL-2R levels are considered a favorable biomarker for anti-TNFα response, as they indicate reduced T-cell activation and lower systemic immune activity (Kuuliala et al., 2006).

Other potential biomarkers under investigation include Cochlin (a protein associated with hereditary deafness DFNA9), anti-cochlin antibodies, myelin p0, β-tectorin, and COCH5B2 proteins. However, these markers have limited sensitivity and specificity, and none are used in routine clinical practice (Boulassel et al., 2001; Matsuoka and Harris, 2013). Similarly, tests like lymphocyte migration inhibition assays and lymphocyte transformation tests have undetermined diagnostic accuracy (Mijovic et al., 2013).

Given the greater understanding of genetic causes of autoimmunity and IMIED we now recommend the use of whole genome sequencing in selected patients, particularly in those with other features of autoimmune disease that is currently undiagnosed.

BOX 1 Proposed diagnostic criteria for Immune Mediated Inner Ear Disease (IMIED).

Certain IMIED – SNHL or peripheral vestibular dysfunction that reverses with immunomodulatory treatment and relapses with withdrawal of immunomodulatory treatment and reverses again with recommencement of immunomodulatory treatment.

Probable IMIED - SNHL or peripheral vestibular dysfunction that reverses with immunomodulatory treatment and relapses with withdrawal of immunomodulatory treatment.

Possible IMIED - SNHL or peripheral vestibular dysfunction that reverses with immunomodulatory treatment or fluctuating SNHL or peripheral vestibular dysfunction or SNHL or peripheral vestibular dysfunction in the presence of a detected immune marker.

Due to the limitations of current diagnostic criteria and the lack of definitive biomarkers, we propose a new classification system that better reflects the diversity of clinical presentations in IMIED. This framework would help clinicians identify more patients as "possible IMIED" and then trial immunomodulatory treatments to further confirm the diagnosis. Although the presence of diagnostic biomarkers is not necessary for treatment, clinical criteria should guide the initiation of immunomodulatory therapies (Box 1).

7 Treatment approaches

The management of IMIED requires a multidisciplinary approach, bringing together specialists from various fields, including otologists, audiologists, immunologists, and potentially rheumatologists and dermatologists. This collaboration is crucial as 15–30% of IMIED patients may present with concurrent systemic immune features or develop these features over time (Mijovic et al., 2013). The involvement of rheumatology and immunology is particularly important to ensure appropriate clinical management, prescribing, and ongoing workup for immunomodulatory therapies.

From the neurotologist's perspective, the primary focus of management revolves around addressing hearing and vestibular impairments. However, many patients with IMIED also experience tinnitus, which can significantly impact their quality of life. Tinnitus management in IMIED often occurs alongside efforts to improve hearing function and includes traditional tinnitus management approaches. For concomitant vestibulopathy, treatment follows a similar multidisciplinary approach, aligning with how other vestibulopathies are managed in neurotology (Mendis et al., 2022). The collaborative care model ensures that patients receive comprehensive and coordinated treatment, optimizing both their hearing and balance while addressing the underlying immune dysregulation that causes the disease.

7.1 Pharmacological interventions

Corticosteroids are the first-line treatment for IMIED, primarily due to their effectiveness, affordability, and wide availability. They have an initial response rate of 50–70%

TABLE 2 Systemic steroids used in the management of IMIED.

Systemic steroid	Dose	Mechanism	Bioavailability	Glucocorticoid: mineralocorticoid	Duration of action (hours)	Therapeutic indication
Prednisone	1 mg/kg/day	Inhibits proinflammatory cytokine production. Suppression of the migration of polymorphonuclear leukocytes and reverses increased capillary permeability Inhibits the phospholipase A2 enzyme Effect on inner ear ion homeostasis	62% (Garg and Jusko, 1994)	4:0.8	12–36	Anti-inflammatory and immunosuppressant Mineralocorticoid effect may have additional benefit in inner ear ion homeostasis (Puckett et al., 2024)
Dexamethasone	12 mg/day	Inhibits proinflammatory cytokine production Suppression of the migration of polymorphonuclear leukocytes and reverses increased capillary permeability Inhibits the phospholipase A2 enzyme	81% (Spoorenberg et al., 2014)	30:minimal	36–72	High glucocorticoid activity makes it a useful anti-inflammatory/ immunosuppressant (Johnson et al., 2024)
Methylprednisone	48 mg/day	Inhibits proinflammatory cytokine production. Suppression of the migration of polymorphonuclear leukocytes and reverses increased capillary permeability Inhibits the phospholipase A2 enzyme Effect on inner ear ion homeostasis	89.9% (Garg et al., 1979)	5:0.5	12–36	Anti-inflammatory and immunosuppressant Mineralocorticoid effect may have additional benefit in inner ear ion homeostasis (Ocejo and Correa, 2024)

in IMIED cases (Sakano and Harris, 2018). The action of corticosteroids is believed to be mediated via glucocorticoid receptors in the inner ear, which leads to downregulation of cytokines, inflammation, and antibody production (Breslin et al., 2020). Steroids with mineralocorticoid effects (e.g., prednisone and methylprednisolone) may also help by improving ion homeostasis in the inner ear, offering additional benefits in steroid-responsive hearing loss (Trune et al., 2006) (Tables 2, 3).

7.1.1 Steroid protocol

A typical initial steroid regimen involves a trial of 1 mg/kg (up to 60 mg) of prednisone for 4 weeks. If no response is observed, the steroid is tapered over 2 weeks. If a response is noted, the dose is tapered over 4 weeks, carefully monitoring for relapse. In the event of relapse, the dose is reinstated to 60 mg and the patient is reviewed by an immunologist for possible switch to another immunomodulatory agent (Alexander et al., 2009; Rauch, 1997). In some cases, patients may remain on low-dose maintenance steroids, potentially combined with other therapies or pulsed high-dose steroids for short-term relapses.

Despite their initial effectiveness, long-term steroid use raises concerns due to side effects such as mood changes, mania, depression, weight gain, insomnia, and a rare risk of hip necrosis (Liu et al., 2017). In a study of 116 patients on a 1-month course of prednisone, 6% had to discontinue due to adverse effects, with hyperglycemia being the most common. Chronic side effects include osteoporosis, diabetes, cardiovascular issues, gastrointestinal disturbances, immunosuppression, and psychiatric disturbances (Liu et al., 2017).

7.1.2 Transtympanic steroids

With an understanding of pharmacokinetics to the inner ear, we routinely co-prescribe transtympanic steroids with oral steroids. Overall, steroids delivered through the middle ear and via the round window lead to larger steroid concentration in the perilymph and cochlear tissue when compared with systemic administration where the blood labyrinthine barrier needs to be overcome (Wang et al.,

TABLE 3 Transtympanic steroids used in the management of IMIED.

Transtympanic steroid	Dose	Mechanism	Inner ear pharmokinetics
Dexamethasone phosphate	4–24 mg/ml	Phospholipase A2 inhibition. Reduce proinflammatory cytokines. Reduce lymphocyte migration and capillary permeability. Mineralocorticoid effect on inner ear ion homeostasis.	Perilymph concentration only reaches 0.13 % of the applied concentration due to slow entry to the inner ear because of the addition polar phosphate group (that increase solubility) and rapid loss to the inner ear vasculature. Results in poor distribution to apical cochlea (Salt et al., 2018).
Methyl prednisone-succinate/hemisuccinate (Solumedrol)	20–125 mg/ml	Phospholipase A2 inhibition. Reduce proinflammatory cytokines. Reduce lymphocyte migration and capillary permeability. Mineralocorticoid effect on inner ear ion homeostasis.	Pharmokinetics not yet determined. No evidence to date that methylprednisone derivatives are metabolized to the active methylprednisone in the inner ear.
Triamcinolone acetonide	40 mg/ml	Phospholipase A2 inhibition. Reduce proinflammatory cytokines. Reduce lymphocyte migration and capillary permeability. No mineralocorticoid action.	Triamcinolone is a suspension with particles in the 1–5 micrometer size range that are too large to cross the round window membrane. Deposition of these particles onto the round window may allow for a time-release steroid delivery mechanism of as the particles dissolve (Mikulec et al., 2008).

2018; Yang et al., 2008). Transtympanic steroids enter through the round window and, as expected, demonstrate a significant base to apex gradient with a higher concentration at the base in perilymph and inner ear tissue (Creber et al., 2018). The basal regions of the cochlear are exposed to five hundred fold the steroid concentration compared to the apex, with the overall concentration being around two fold higher in the perilymph with transtympanic delivery (Salt and Hirose, 2018; Bird et al., 2007, 2011). In comparison oral steroids, demonstrate an apex to base gradient with higher concentrations at the apex (Creber et al., 2018). Interestingly, despite the large differences and gradients between transtympanic and systemic delivery, there is similar levels of glucocorticoid receptor activation across the regions of the inner ear (Creber et al., 2018). In short, the two modes of delivery should not be seen as alternatives, rather they should be seen as complementary. If the aim to maximize steroid concentration in the inner ear tissue for a more "complete cochlear coverage," both routes of delivery should be used, until further research is performed. What is not known is whether the increased concentration of steroids in the inner ear is clinically significant over one route alone. Matsuoka et al. reported that 50% (15/30 AIED patients) demonstrated hearing improvement with intratympanic steroids, although it is uncertain from the report if these patients received other treatments (Matsuoka and Harris, 2013). García-Berrocal et al. (2006) demonstrated 6/11 patients with AIED treated with intratympanic methylprednisone showed improved hearing thresholds. Additionally, there have been small case series reporting that intratympanic steroids can be effective in the management of AIED induced by immune checkpoint inhibitors and adoptive cell immunotherapy for cancer (Zibelman et al., 2016; Johnson et al., 2009).

Commercially available steroid solutions of methylprednisolone, dexamethasone and triamcinolone are formulated with ~8.8 mg/ml benzyl alcohol which has been shown to increase round window penetration (Mikulec et al., 2008). There is controversy over which steroid is the best use for transtympanic delivery. Unfortunately, the majority of clinical studies in this area do not take advantage of the highest available doses. When considering steroid injection via the transtympanic route, factors such as available dosage, anti-inflammatory potency, and round window membrane permeability should be taken into consideration. Anecdotally, methylprednisolone may be uncomfortable to patients in the middle ear and has traditionally been diluted with sodium bicarbonate prior to injection (Dallan et al., 2006; Berjis et al., 2016). Dexamethasone is the most studied but likely the poorest of the options for round window penetration (Salt and Plontke, 2018). If selecting for the highest dose commercially available to deliver the highest anti-inflammatory effect with the best likely round window penetration then the choice should be triamcinolone at 24 mg/ml, followed by methylprednisolone at 80 mg/ml. Higher concentrations may also be available outside of the United States and change the decision making to favor a different choice so clinicians should be aware of the doses available and anti-inflammatory potency of the steroids available to them. Unfortunately, most of the comparison studies in this area are non-randomized or non-blinded and have failed to consistently show clinically significant differences (Emami et al., 2023). A proposed initial treatment algorithm is shown in Figure 5.

7.1.3 Cytotoxic chemotherapy and biologic agents

Beyond oral and intra-tympanic steroid treatments, cytotoxic chemotherapeutic agents (e.g., methotrexate, mycophenolate, and azathioprine) and biologics have been trialed in IMIED (Table 4, Figure 3).

Methotrexate, an antifolate antimetabolite and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) inhibitor, is a disease modifying treatment that is used in a number of autoimmune conditions. It works through several mechanisms, including TNF, IL-1 inhibition, IL-10 upregulation and modulation of NFkB and immune cell adenosine signaling (Friedman and Cronstein, 2019). A randomized control trial of 67 patients with AIED examined whether methotrexate could be used to maintain hearing improvement achieved with prednisone. However, methotrexate was not more effective than placebo in

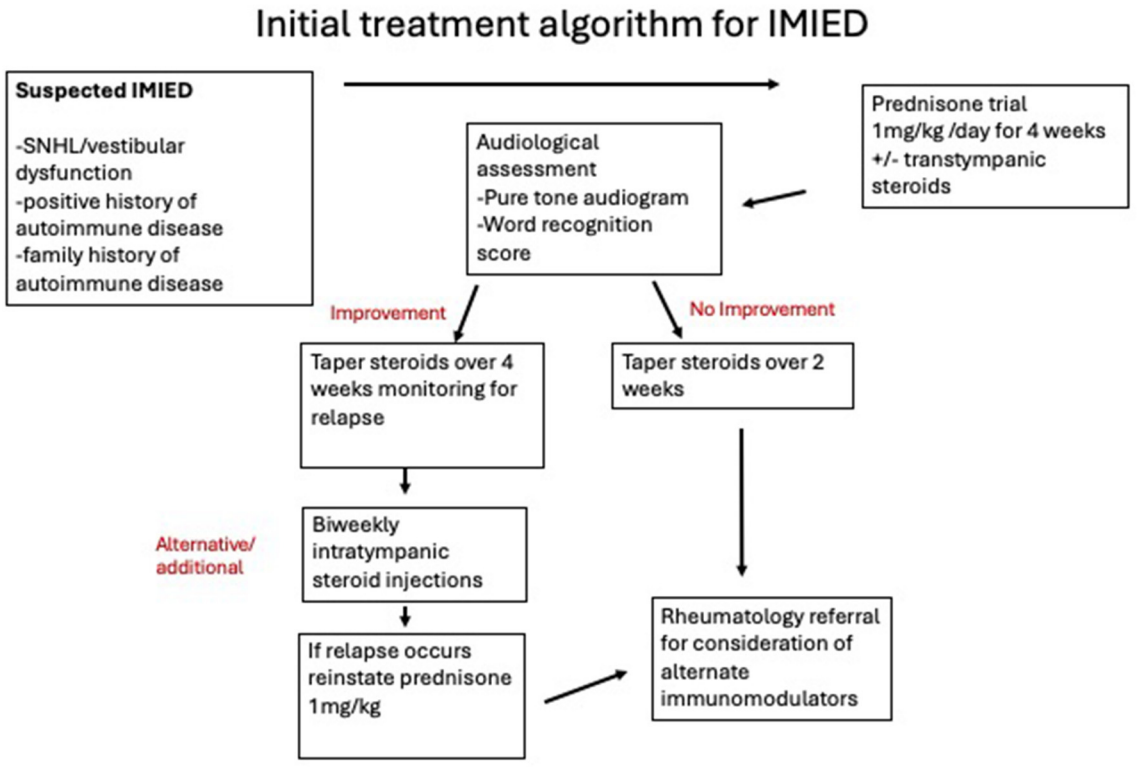

FIGURE 5
Proposed initial treatment algorithm for IMIED.

this regard (Harris et al., 2003). A combination of methotrexate and azathioprine demonstrated low and mid tone improvement in hearing in a patient with AIED (Huang et al., 2023). Mycophenolate is an immunosuppressant primarily via its inhibition of *de novo* purine synthesis in lymphocytes. Clinically it is used to prevent organ transplant rejection and autoimmune conditions including Crohn's disease, lupus, and small vessel vasculitides. Although not studied in larger trials, there have been reports of the successful use of mycophenolate as a steroid sparing agent in Cogan's syndrome (Hautefort et al., 2009).

Cytotoxic chemotherapeutic agents however carry significant systemic risks including increased risk of lymphoma, myelosuppression and teratogenicity (Katherine et al., 2023). There is therefore increasing interest in biologic agents including TNF-α inhibitors (etanercept, infliximab, adalimumab, and golimumab), CD20 inhibitors (rituximab) and IL-1 inhibitors (anakinra and canakinumab) (Figure 3). These classes of immunotherapies are likely to have the greatest impact in the near future for the treatment of IMIED.

TNF alpha is a cytokine that plays a critical role in cellular inflammation and the regulation of immune cells. Additionally, it acts an endogenous pyrogen that can induce fever, apoptosis and inhibit tumor growth. Aberrant TNF signaling has been implicated in several disease states including autoimmune conditions such as rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease (Jang et al., 2021). TNF is not detected in the normal cochlea but can be upregulated by cellular stress, including aging and acoustic trauma and hence TNF alpha has been shown to play a role in SNHL, possibly by altering cochlear blood flow (Arpornchayanon et al., 2013). Intracochlear perfusion of KLH causes an influx of immune cells, alteration in cochlear blood flow and an increase in TNF alpha which was reversed on administration of etanercept, a TNF alpha antagonist (Satoh et al., 2002). Etanercept is a human fusion protein composed of the Fc portion of IgG1 and extracellular ligand-binding domain of the TNF p75 receptor. It is currently indicated for the treatment of autoimmune diseases including rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (Jang et al., 2021). It is a common first biologic agent choice for AIED, and our preferred first option, given it is widely used, inexpensive and can be administered by injection 1-2 times per week without the requirement to monitor drug levels. Before starting therapy, Hepatitis B and Quantiferon testing are performed. There is an increased risk of infection, allergic reactions and induced psoriasis and patients should be cautioned that resistance may develop requiring treatment discontinuation. In the future it is hoped there will be biomarkers that may be used to predict response, as shown by the use of HLA Cw06 testing for the response to ustekinumab (Chiu et al., 2014). A retrospective case series of 12 AIED patients refractory to corticosteroids treated with etanercept twice weekly for 6 months demonstrated improvement or stabilization of hearing in 92% of patients (Rahman et al., 2001). However, a further cohort study contradicted these results, demonstrating that etanercept was no better than placebo for treating AIED hearing loss (Cohen et al., 2005). Cogan syndrome has been primarily treated with corticosteroids although more recently infliximab, an anti-TNF

TABLE 4 Non-steroidal immunomodulatory drugs used for IMIED.

Drug	Brand names	Target	Dose	Approved indication	Workup	Adverse effects	Monitoring
Methotrexate	Trexall, Reditrex, Xatmep	Folic acid antagonist (cytotoxic) AICAR transformylase inhibitor (immunosuppression)	7.5–17.5 mg/week orally	Rheumatoid arthritis, SLE, psoriasis, connective tissue disorders, IBD, chemotherapy	CBC with differential, renal function, blood urea nitrogen, urinalysis, liver function tests, hepatitis serology, HIV testing, TB testing	Nausea, vomiting, mucosal ulcers, and loss of appetite, hepatotoxicity	Monitoring of CBC, serum creatinine, and transaminases is recommended weekly for the first 4 weeks and then at least bimonthly
Mycophenolate	CellCept, Myfortic, MMF	Inosine monophosphate dehydrogenase inhibitor	2,000–3,000 mg/day orally	Crohn's disease, Lupus, Behcet disease, post transplant immunosuppression	CBC with differential, renal function, blood urea nitrogen, urinalysis, liver function tests, hepatitis serology, HIV testing, TB testing	Nausea, infections, diarrhea, anemia, GI bleeding, leukoencephalopathy, hepatitis	Monitor CBC, LFTs, monitor for signs of infection
Etanercept	Enbrel, Erelzi, Eticovo	Soluble receptor that binds both TNF-alpha and TNF-beta, TNF inhibitor	25 mg twice weekly by subcutaneous injection	Ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis	CBC with differential, renal function, blood urea nitrogen, urinalysis, liver function tests, hepatitis serology, HIV testing, TB testing	Infection, aplastic anemia, blood dyscrasias, GI/liver disorder, skin reactions	Monitor for signs of infection, hepatitis, hypersensitivity, malignancy and lupus like disorder
Adalimumab	Humira, Amgevita, Hyrimoz	Recombinant immunoglobulin G (IgG) anti-TNF-α mAb	40 mg every 2 weeks subcutaneous injection	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn disease, and ulcerative colitis	CBC with differential, renal function, blood urea nitrogen, urinalysis, liver function tests, hepatitis serology, HIV testing, TB testing	Injection site reactions, headache, rash, and upper respiratory tract infections. Reactivation of latent infections (TB), lymphoma	CBC and liver function tests and assessing serum urea and electrolytes at baseline, followed by monthly assessments for the first 3 months and subsequently every 3 months. Annual screen for anti-dsDNA
Golimumab	Simponi, Simponi Aria	Recombinant immunoglobulin G (IgG) anti-TNF-α mAb	0.3 ml golimumab standard solution intratympanic at 0,1,3,5 weeks.	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and ulcerative colitis	None required with intratympanic administration	No side effects reported from intratympanic use	None required
Infliximab	ASOLVA, Inflectra, Remicade	Recombinant immuoglobulin G (IgG) anti-TNF-α mAb	0.3 ml infliximab standard solution intratympanic once a week for 4 week	Crohn's, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis	None required with intratympanic administration	No side effects reported from intratympanic use	None required
Anakinra	Kineret	Blocks the binding of IL-1 alpha and IL-1 beta, to the interleukin-1 type 1 receptor	100 mg subcutaneous injection	Rheumatoid arthritis, neonatal-onset multisystem inflammatory disease, deficiency of interleukin-1 disease	CBC with differential screening, hepatitis serology	Infections, allergic reaction, neutropenia, headache, nausea, vomiting	Check neutrophil count before initiation followed by monthly for the first 3 months of therapy, and then quarterly for up to 1 year
Rituximab	Riabni, Rituxan, Truxima	Anti-CD20 antibody	Two infusions of 1,000 mg intravenous spaced 1–8 days apart	CD20 positive B-cell Non-Hodgkin's Lymphoma, CLL, Rheumatoid arthritis, Pemphigus vulgaris	CBC, routine chemistries, serum immunoglobulin levels, chest X-ray, and serologic testing for hepatitis B, C, and HIV should be obtained	Infections, infusion reactions, renal failure, arrythmias, lymphopenia	CBC, electrolytes, renal function, serum immunoglobulin, cardiac monitoring, liver function tests
Canakinumab	Ilaris	Blocks the binding of IL-1 beta, to the interleukin-1 type 1 receptor	150 mg or 2 mg/kg canakinumab every 8 weeks.	Periodic fever syndromes, Stills disease, gout arthritis	CBC with differential screening, hepatitis serology, TB testing	Infections, nasopharyngitis, diarrhea, influenza, rhinitis, headache, nausea, bronchitis, gastroenteritis, hypersensitivity, macrophage activation syndrome	Monitor for infections, neutropenia

AICAR, 5-Aminoimidazole-4-carboxamide ribonucleoside; SLE, Systemic lupus erythematosus; CBC, Complete blood count; HIV, Human Immunodeficiency Virus; TB, Tuberculosis; GI, Gastrointestinal; LFT, Liver Function Test; TNF, Tumor necrosis factor; mAB, monoclonal antibody; dsDNA, double stranded DNA; CLL, Chronic Lymphocytic Leukemia.

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therapy, has demonstrated hearing improvement in 89% of treated patients (Padoan et al., 2019). Other anti-TNF alpha therapies that have been used with limited success in small AIED case series include Adalimumab and Golimumab (Balouch et al., 2022).

IL-1 is a family of 11 cytokines, including IL-1α and IL-1β, that plays a central role in the regulation of inflammatory and immune responses. Patients with IMIED who fail to respond to corticosteroids have been shown to have higher plasma levels of IL-1β than steroid-responsive patients. The mechanistic link between IL-1 and SNHL is uncertain, but IL-1β triggered immune cell infiltration has been suggested (Hashimoto et al., 2005). Additionally, IL-1β increases expression of metalloproteinase-9 in the cochlea, which may cause compromise of the blood labyrinth barrier and stria vascularis (Wu et al., 2017). IL-1β and IL-18 are downstream products of the NLRP3 inflammasome, discussed above, and so IL-1β inhibition has a promising role for macrophage mediated inner ear hearing loss (Xia et al., 2022). Anakinira, an IL-1 receptor antagonist, is currently approved for use in rheumatoid arthritis and neonatal multisystem inflammatory disease. It requires daily injection and may cause thrombocytopenia requiring a full blood count check 4 weeks after starting therapy. It is recommended to order a Hepatitis B panel before starting treatment. Although there is an increased risk of infections with Anakinra use, the half-life of the drug is short, so on treatment discontinuation there is a quick reconstitution of the immune system. In a phase I/II efficacy trial of 10 patients with corticosteroid resistant IMIED, 7 patients treated with anakinra demonstrated improvements in pure tone average and word recognition score with decreased levels of IL-1β correlating with hearing levels (Vambutas et al., 2014). Anakinra has also been used successfully to treat hearing loss in patients with Muckle-Wells syndrome. In a prospective cohort study with 10 patients treated with Anakinra, 5/20 ears showed improvement in hearing thresholds (Kuemmerle-Deschner et al., 2015). This study also demonstrated improvement in 6/26 ears in patients treated with Canakiumab, another IL-1 receptor antagonist.

Although promising, there are multiple aspects of biologic therapies for IMIED that warrant further exploration. These include the study of novel classes of use of biologics, including JNK inhibitors such as tofacitinib and AM-111, in addition to optimizing dosage and administration routes for current therapies (Hu et al., 2021; Balouch et al., 2022).

7.2 Hearing aids and cochlear implants

Hearing aids are the primary treatment for patients with unsalvageable hearing loss due to Immune-Mediated Inner Ear Disease (IMIED). They should be offered to adults whose hearing loss significantly impacts their ability to communicate, hear environmental sounds, or enjoy music. Studies have shown that AIED often leads to cochlear inflammation, which can progress to fibrosis and ossification (Hoistad et al., 1998). One study found that 53.3% of AIED patients had cochlear fibrosis or ossification (Kamakura et al., 2017). This structural damage can severely limit hearing recovery, making hearing aids an essential tool in managing these patients.

Given the risk of cochlear fibrosis, a T2-weighted MRI should be included in the work-up for cochlear implantation to assess the extent of damage and predict potential outcomes. Intracochlear fibrosis can reduce the effectiveness of cochlear implants (Hoistad et al., 1998). In addition, patients with AIED often have an increased risk of immunocompromise, which warrants careful consideration of the risk of meningitis and the need for pneumococcal vaccines prior to surgery.

During surgery, patients on chronic steroid therapy may experience secondary adrenal insufficiency, which could require a preinduction steroid dose to mitigate the risk of adrenal crisis (Goh et al., 2022). Cochlear implant outcomes for AIED patients are generally comparable to those of the general population; however, some patients have experienced progressive deterioration in hearing outcomes. This deterioration appears to correlate with fluctuations in cochlear impedances and the ongoing activity of the systemic disease (Goh et al., 2022). These findings suggest that synaptopathy or dysfunction in the spiral ganglion may play a role in the progressive hearing loss observed in these patients.

8 Conclusions

IMIED is an important, yet often underdiagnosed cause of medically treatable sensorineural hearing loss. Its diagnosis is challenging due to the absence of specific diagnostic tests, and it relies heavily on clinical presentation and disease course, which can overlap with other audiovestibular disorders. While most patients experience disease isolated to the inner ear, up to a third may present with hearing loss as part of a systemic autoimmune disease. A key feature of IMIED is the characteristic response to corticosteroids, which is a determining factor in our new classification. However, some patients may become refractory to steroids, requiring alternative immunosuppressive treatments.

Current evidence suggests that autoantibodies, cytotoxic T cells, or innate immune system mechanisms, or a combination of these, mediate IMIED. With a deeper understanding of the disease's pathological mechanisms, there is hope that the development of novel biomarkers, particularly serum markers that correlate with treatment response, will emerge and become clinically useful.

Although immunosuppressive treatments typically yield positive results for IMIED patients, large, multicenter randomized trials are needed to better evaluate the role of corticosteroids and emerging immunomodulatory drugs. It is critical to establish evidence-based diagnostic and therapeutic guidelines for the management of IMIED. While hearing aids and cochlear implants provide symptomatic relief for patients, the ultimate goal is that novel immunomodulatory treatments will prevent irreversible inner ear damage and preserve hearing in these patients.

Author contributions

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