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AAO: Autoimmune and Autoinflammatory (Disease) in Otology: What is New in Immune-Mediated Hearing Loss

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Objectives: Autoinflammatory diseases are a family of immune-mediated, rare diseases, some of which, exhibit sensorineural hearing loss (SNHL), suggesting potentially similar mechanisms of molecular pathogenesis between autoinflammatory-mediated hearing loss and autoimmune inner ear disease (AIED) may exist. The purpose of this review is to compare the clinical features of autoimmune and autoinflammatory diseases that affect hearing, discuss the limitations of our knowledge, and highlight potential new disease mechanisms and therapeutics.

Data sources: Pubmed Literature Review; Google Scholar Literature review.

Review methods: A focused comparison of AIED with a number of autoinflammatory diseases that manifest with sensorineural hearing loss was performed. The pathogenesis of these diseases is reviewed in the context of the innate and adaptive immune system, cytokine expression and genetic polymorphisms.

Results: AIED, since first described by Cogan and Lehnhardt and first clinically characterized by McCabe, has remained an enigmatic disease, with limited advances in both new diagnostics and new therapeutics. Since the discovery of autoinflammatory diseases, a number of systemic autoimmune diseases have either been re-classed as autoinflammatory diseases or identified to have features of autoinflammatory disease.

Conclusion: AIED has clinical features of both autoimmune and autoinflammatory disease. It is critical that autoinflammatory diseases be correctly identified, as failure to do so may result in systemic amyloidosis and kidney damage.

INTRODUCTION

Autoinflammatory diseases are a family of immune-mediated rare diseases, some of which exhibit sensorineural hearing loss (SNHL) suggesting that potentially similar mechanisms of the molecular pathogenesis of hearing loss may exist. Since the discovery of autoinflammatory diseases, a number of autoimmune diseases have either been re-classed as autoinflammatory diseases or identified to have features of autoinflammatory disease. It is critical that autoinflammatory diseases be correctly identified because failure to do so may result in systemic amyloidosis and kidney damage. The purpose of this review is to compare the clinical features of autoimmune and autoinflammatory diseases, discuss the limitations of our knowledge, and highlight potential new disease mechanisms and therapeutics.

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MATERIALS AND METHODS

History of Autoimmune Inner Ear Disease

Autoimmune inner ear disease (AIED) was first described by Cogan in the 1940s[1] and Lehnhardt in the 1950s,[2] and a limited series of patients benefitted from a combination of steroids and cyclophosphamide, as noted by McCabe in the 1970s.[3] Described by investigators as a bilateral SNHL with a decline in at least one ear evolving in greater than 3 days but less than 90, response to steroids has been a requisite clinical criterion for diagnosis.[4] More specifically, however, response to steroids was used as an entrance criterion to test steroid-sparing biologic therapies in clinical trials such as methotrexate[4] and etanercept.[5] The rationale for this approach was the natural history of this disease as a progressive SNHL, at risk for further hearing decline in the absence of therapy. Although an initial clinical response to steroids has helped to define AIED, for those with repetitive declines in hearing necessitating corticosteroid treatment, only 14% remain corticosteroid-responsive after 34 months.[6] Development of corticosteroid resistance is common in many autoimmune and autoinflammatory diseases: for example, 30% of rheumatoid arthritis patients,[7] up to 57% of lupus nephritis patients,[8] and up to 40% of ulcerative colitis patients[9] are corticosteroid-resistant. The incidence of AIED is significantly lower than the rate of acute SNHL, which occurs at a rate of five to 20 cases per 100,000 per year.[10] If we extrapolate the prevalence from this, we would calculate that the incidence is less than five cases per 100,000 per year. Furthermore, the duration of time from initial presentation to development of refractory disease that may only be managed with rehabilitative strategies, such as hearing aids or cochlear implants, is 34 months because only 14% remain corticosteroid-responsive at this interval. Thus, using the formula prevalence = incidence $\times$ duration, we get $P = 5/100{,}000/\text{year} \times 3 \text{ years} = 15/100{,}000$. Because there are approximately 300,000,000 persons in the United States, the prevalence at any time is approximately 45,000 persons with AIED. Therefore, AIED is a yet-to-be classified orphan disease.

TABLE I.
Characteristics of Autoimmune Versus Autoinflammatory Disease

	Autoimmune	Autoinflammatory
Type of immune reaction	Adaptive	Innate
Autoantibodies	High titer	Low titer/ nonspecific
Cytokines	IL-17, Interferon-gamma, TNF	IL-1
Predominant cell type dictating response	T cells	Monocytes
Anti-cochlin antibodies	High titer[27]	Low titer[15]

IL = interleukin; TNF = tumor necrosis factor.

Pathogenesis of Autoimmune Inner Ear Disease

As with most autoimmune diseases, it has been postulated that a misdirected attack on self, in this case to inner ear proteins, results in both proinflammatory T-cell responses and autoantibody formation, which represent the basic features of AIED and other autoimmune diseases. Unlike other autoimmune diseases in which a single autoantibody dominates, the presence of autoantibodies in AIED is inconsistent, with no single autoantibody diagnostic or prognostic for therapeutic response. In the mid-1990s, discovery of 68kD protein, which was identified to be an antibody to heat shock protein 70 (HSP70) in patients with AIED and Meniere disease, was thought to be predictive of steroid responsiveness.[11] Not surprisingly, HSP70 is likely a bystander molecule because HSPs are a conserved family of proteins expressed during cellular stress. A second study demonstrated that only 9% of patients with AIED were HSP70-positive.[12] Moreover, HSP70 antibodies have subsequently been detected in controls at a rate similar to controls, reducing the utility of HSP antibodies in the diagnosis of AIED.[13] Similarly, other autoantibodies have been described; however, none have been specific to AIED, although the presence of anti-cochlin antibodies has been shown in a small cohort and would represent a cochlear specific antibody response.[14,15]

Much of the early, instrumental experimental work in this field was established by Ryan, Harris, Keithley, Gloddek, Tuohy, Hughes, and others.[16–20] Given the difficulties of accessing the human cochlea, much of our early understanding was gleaned from a guinea pig model inoculated with Keyhole limpet hemocyanin (KLH), a strong immunogen capable of inducing labyrinthitis.[21,22] Although this model was exceptionally useful to mechanistically describe immune reactions in the inner ear, it was a limited surrogate for identifying therapeutic interventions for human immune-mediated hearing loss because what worked in this model[23] did not in fact work in humans with the disease.[24] Studies of AIED have been difficult, however, because 1) the cochlea has limited access for clinical study; 2) studies of the peripheral blood immune system may not be indicative of the immune reactions in the inner ear; and 3) early studies in guinea pigs had limited immunologic reagents available for characterization of complex immune system reactions. The basic tenet of any animal model to be representative of human autoimmune disease is that the disease must be recapitulated in an animal model according to Witebsky's postulates.[25] In 2004, the murine cochlin-peptide vaccination model was described that validated AIED as an autoimmune disease,[26] and a cohort of patients were identified to have high titer anti-cochlin antibodies[27] (Table I). Overall, human studies in AIED have been limited, with a lack of consistent studies supportive of autoimmune disease. Although high titer, cochlin-specific antibodies have been observed; we have noted low titer anti-cochlin antibodies in a cohort AIED patients, which is more consistent with an autoinflammatory disease[28]; and others have seen inconsistent autoantibodies.[29] In support of an autoimmune disease, evidence of proinflammatory T cells that secrete interleukin-17 (IL-17)[28] and interferon-gamma[30] exist, and patients with naïve T cells had a better prognosis than those with memory T cells.[30] Is this a result of limited access into the human cochlea to better characterize the molecular events of immune-mediated hearing loss, or is it the result of comingling of other disease processes that resemble an autoimmune disease? The difficulties of identifying consistent autoantibodies, coupled with the observations of T cells releasing IL-17 and interferon-gamma, are suggestive that AIED has features of both autoimmune disease and autoinflammatory disease. Similarly, a number of autoimmune diseases such as rheumatoid arthritis have features suggestive of both autoimmune and autoinflammatory disease.[31]

Standard Therapies for Autoimmune Inner Ear Disease

The mainstay of treatment for AIED has been corticosteroids, which have been used in varying doses and for varying duration. During the serial audiometry trial for AIED, therapy consisted of high-dose corticosteroids for a minimum of 28 days.[32] Despite this aggressive regimen, although a statistically significant gain in hearing was achieved, the magnitude of the gain was relatively small at a 4-dB PTA average improvement and an 8% average improvement in word recognition scores.[32] Since the time of these studies, the advent of intratympanic corticosteroid therapy has become commonplace, which through a large clinical trial for sudden SNHL we know to be equally efficacious to oral corticosteroids.[33] It remains to be shown whether oral or intratympanic steroids are more efficacious or whether other distinct advantages exist for use in AIED. Methotrexate was evaluated in a multicentered clinical trial as a potential steroid-sparing agent in corticosteroid-responsive patients.[4] This therapy failed to exceed the placebo response. Methotrexate used as monotherapy is inferior to use in combination with a tumor necrosis factor (TNF) inhibitor in rheumatoid arthritis,[34] and as such it still may hold promise when used in combination with other immunosuppressives in AIED. Use of immnuosuppressives that block specific preinflammatory cytokines have been explored with varying success, as discussed below.

Cytokines and Autoimmune Inner Ear Disease

Early expression of cytokines during the innate immune response will often dictate many of the later adaptive immune responses in AIED. The role of cytokines in the autoimmune process has been investigated in both animal models and in human disease (see Table II). In a murine model, using KLH as a stimulus, TNF was identified as a key cytokine instigating an adaptive immune response.[35] Similarly, in humans with immune-mediated hearing loss, we identified elevated TNF levels to be largely predictive of steroid-sensitive, immune-mediated hearing loss.[36] Tumor necrosis factor antagonism appears to have therapeutic benefit in Cogan syndrome patients[37] and several other small cohorts with AIED by intratympanic injection[38,39]; however, in another placebo-controlled study of successful corticosteroid-treated AIED patients, TNF antagonism by intravenous infusion was no better than placebo.[24] Why is there a disparity? Potentially timing of treatment relative to corticosteroid use, type of TNF antagonist used, and/or the route of administration may explain this apparent difference in response. Experimentally, we have observed that peripheral blood immune cells from steroid-sensitive patients release high levels of TNF in vitro culture, and

TABLE II.
Cytokine Expression and Immune Mediated Hearing Loss.

Disease	Cytokine Expression	Effect on Disease
Steroid-sensitive AIED	TNF	Reduction in TNF correlates with steroid response[59]
Steroid-resistant AIED	IL-1	Reduction of IL-1 with correlates results in improved hearing in limited series of patients[60]
Cogan syndrome	TNF	Induces remission of disease in a few cases[61,62]
Meniere disease	MIF genetic polymorphism? [63,64]	Unknown
SNHL	IL-1 genetic polymorphisms[65]	Unknown
	MIF genetic polymorphisms	MIF polymorphisms correlate with steroid responsiveness[66]
Noise-induced hearing loss (animal results only)	MIF gene; IL-6	MIF knock-out mice fail to recover hearing after noise exposure[67] IL-6 blockade improves cochlear blood flow in NIHL animal model[68]

AIED = autoimmune inner ear disease; IL = interleukin; MIF = migration inhibitory factor; NIHL = noise induced hearing loss; SNHL = sensorineural hearing loss; TNF = tumor necrosis factor.

this is dramatically reduced with dexamethasone. Perhaps initial use of corticosteroids prior to TNF inhibition resulted in excessive reduction of the intended molecular target and compromised efficacy in the placebo-controlled trial.

Interleukin-1 was initially discarded as a potential mediator of immune reaction in the inner ear in several animal models. In the labyrinthitis model, it was interpreted to be expressed in response to surgical trauma.[40] Furthermore, aggressive inhibition of IL-1 using its receptor antagonist resulted in spiral ganglion cell loss in another animal model.[41] The role of IL-1 in animal models and human disease turned out to be quite disparate. In humans, differential expression of the IL-1, nonsignaling decoy receptor was identified in AIED patients as compared with controls undergoing cochlear implantation.[42] Further studies revealed that IL-1 was elevated in the plasma of patients who failed to respond to corticosteroid therapy,[43] suggesting that failure to respond to corticosteroids may not be antonymous with immune-mediated hearing loss. Finally, in a limited open-label study of IL-1 antagonism with anakinra in corticosteroid-resistant AIED, patients resulted in improvement in pure tone average in seven out of 10 subjects and in speech discrimination in eight out of 10 subjects.[44] These improvements trended with a reduction in plasma IL-1 levels. Interleukin-1 is predominantly produced by monocyte and macrophages. In neuroinflammation, macrophage migration inhibitory factor (MIF) is produced and has been suggested to have a putative role in sudden SNHL, Meniere disease, and noise-induced hearing loss (see Table II). Migration inhibitory factor has been demonstrated as an essential mediator for the production of IL-1b, IL-6, and TNF in microglia.[45] Recent animal studies suggest that MIF is a key molecule in the development of glucocorticoid resistance in experimental autoimmune encephalomyelitis (EAE), the animal model of

TABLE III.
CAPS Diseases With Associated Hearing Loss.

Autoinflammatory Disease	Clinical Features	Genetic Mutation/ Inheritance	Treatment	Hearing Loss Manifestation
Muckle-Wells disease	Skin rashes, fever, hearing loss, conjunctivitis, amyloidosis	NLRP3 (also called CIAS1)/AD	IL-1 inhibitors	High-frequency SNHL in 100%, below 4 kHz involved in > 70%, starting in adolescence[54]
NOMID/CINCA	Fever, meningitis, joint damage, hearing loss, vision loss, uveitis, papilledema	NLRP3 (also called CIAS1)/AD	IL-1 inhibitors	SNHL starting in infancy/ young childhood
Familial cold autoinflmmatory syndrome (FCAS)	Cold-induced urticarial rash, conjunctivitis	NLRP3 (also called CIAS1)/AD	IL-1 inhibitors	? mild SNHL, unclear if disease-related
Monarch-1	Cold-induced uriticarial or malar rash	NLRP12/AD		In 2 of 5 patients, type not defined[69]
H syndrome, also referred to as SLC29A3	IDDM, lymphadenopathy mimicking Rosai-Dorfman, hyperpigmentation, phalyngeal flexion contractures	SLC29A3/AR	Limited data: unresponsive to TNF or IL-1 inhibitors[70]	SNHL from early infancy/ childhood in 53% of patients, average age of onset = 5.9 years[71]

AD = autosomal dominant; AR = autosomal recessive; AIED = autoimmune inner ear disease; CAPS = cyropyrin-associated periodic syndrome; CINCA = chronic infantile neurological, cutaneous, and articular (CINCA) syndrome; FCAS = familial cold autoinflammatory syndrome; IL = interleukin; MIF = migration inhibitory factor; NLRP3 = NACHT, LRR and PYD domains-containing protein 3; NOMID neonatal onset multisystem inflammatory disease; SNHL = sensorineural hearing loss; TNF = tumor necrosis factor.

multiple sclerosis,[46] although glucocorticoid resistance has been attributed to multiple factors including glucocorticoid receptor functional impairment or local factors that impair glucocorticoid availability.[47]

Autoinflammatory Diseases

During the same time, discoveries concerning the mechanisms of AIED were being described, a family of rare autoinflammatory diseases that were exquisitely sensitive to IL-1 inhibition was also being described, largely in the rheumatology literature (as reviewed[48]). Here, genetic mutations/polymorphisms, inherited in an autosomal dominant (AD) manner resulting in a gain of function mutation in a gene called NLRP-3 (also called CIAS-1), resulted in excessive IL-1 beta release, SNHL, systemic amyloidosis, and transient skin rashes. This syndrome, Muckle-Wells, was characterized by a dermatologist in the late 1970s[49] and attributed to excessive IL-1 release.[50] Muckle-Wells syndrome (MWS) and NOMID (neonatal onset multisystem inflammatory disease) belong to a family of autoinflammatory diseases called cyropyrin-associated periodic syndrome (CAPS), some of which include SNHL in their presentation (see Table III for CAPS diseases with associated hearing loss). Of all of the CAPS diseases, MWS is the one most likely associated with SNHL. Interestingly, although case reports exist as to hearing improvement with IL-1 antagonism,[51] initial descriptions of the hearing improvement observed largely were believed to be minimal.[52] Furthermore, as more studies of this rare disease surfaced, several paradigm shifts occurred relative to both inheritance of MWS and hearing amelioration with IL-1 antagonism. Although initially described as AD, in a recent review of CAPS, 133 of the 136 patients studied carried a heterozygous germline mutation, and 42% of these patients had SNHL.[53] In a series of patients with MWS (52% of whom were children), 100% exhibited high-frequency SNHL (equal to or above 6 kHz), whereas 74% were affected from 500 to 4,000 Hz, and all had normal caloric function. Interleukin-1 inhibition resulted in stable or improved hearing in 96% of the patients, although improvement was noted in only 24% and was worsening in 4%.[54] Interestingly, MWS may also comprise neurologic sequelae, including migraine, despite a negative magnetic resonance imaging; symptoms were controlled with IL-1 antagonism.[55] Other rare autoinflammatory diseases, such as Monarch-1 and H syndrome, include SNHL as part of their presentation, most of which initially manifest during childhood (Table III). Interestingly, similar to congenital SNHL for which renal involvement may be seen in conjunction with SNHL, here up to 25% of patients with Muckle-Wells may present with either renal insufficiency or proteinuria, and also may have amyloid deposits noted on kidney biopsy.[56] Additionally, similar to Cogan disease, keratitis has been reported in MWS.[57] Development of corticosteroid resistance in autoinflammatory diseases has been reported. In Behcet disease, now considered an autoinflammatory disease, corticosteroid resistance has been effectively managed with anti-TNF therapy.[58] Notably, the small series of corticosteroid-resistant patients who we treated with anakinra were sequence-negative for the MWS mutation (not shown).

CONCLUSION

With the discovery of autoinflammatory diseases that may manifest with SNHL, our understanding of the putative role of IL-1 and other proinflammatory cytokines involved in the pathogenesis of SNHLwill continue to grow. Multiorgan involvement in many of these rare autoinflammatory diseases has led to a mechanistic understanding of the role IL-1 in various organs, as well as study through large clinical trials of the effect of IL-1 in common diseases such as diabetes and myocardial infarction. Hopefully, this collective knowledge will lead to new therapeutics in AIED and other immune-mediated hearing losses.

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