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

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**INTRODUCTION**

Autoinflammatory diseases are a family of immune-mediated rare diseases, some of which exhibit sensorineural hearing loss (SNHL) suggesting 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.

**MATERIALS AND METHODS**

**History of Autoimmune Inner Ear Disease**

Autoimmune inner ear disease (AIED) was 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 autoimmune diseases or identified to have features of autoimmune 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.
Pathogenesis of Autoimmune Inner Ear Disease

As with most autoimmune diseases, it has been postulated that a misguided 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. 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.

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. 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. 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. 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. 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, and as such it still may hold promise when used in combination with other immunosuppressives in AIED. Use of immunosuppressives 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. Similarity, in humans with immune-mediated hearing loss, we identified elevated TNF levels to be largely predictive of steroid-sensitive, immune-mediated hearing loss. Tumor necrosis factor antagonist appears to have therapeutic benefit in Cogan syndrome patients and several other small cohorts with AIED by intratympanic injection; however, in another placebo-controlled study of successful corticosteroid-treated AIED patients, TNF antagonism by intravenous infusion was no better than placebo. 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...
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. Furthermore, aggressive inhibition of IL-1 using its receptor antagonist resulted in spiral ganglion cell loss in another animal model. 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. Further studies revealed that IL-1 was elevated in the plasma of patients who failed to respond to corticosteroid therapy, suggesting that failure to respond to corticosteroids may not be synonymous with immune-mediated hearing loss. Finally, in a limited open-label study of IL-1 antagonist 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. 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. 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 |
| 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 autoinflammatory 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 urticarial rash, or malar rash | NLRP12/AD | | In 2 of 5 patients, type not defined |
| H syndrome, also referred to as SLC29A3 | IDDM, lymphopenopathy mimicking Rosai-Dorfman, hyperpigmentation, pharyngeal flexion contractures | SLC29A3/AR | Limited data: unresponsive to TNF or IL-1 inhibitors | SNHL from early infancy/childhood in 53% of patients, average age of onset = 5.9 years |

AD = autosomal dominant; AR = autosomal recessive; AIED = autoimmune inner ear disease; CAPS = cryopyrin-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, although glucocorticoid resistance has been attributed to multiple factors including glucocorticoid receptor functional impairment or local factors that impair glucocorticoid availability.

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 antagonism. Many of these diseases have been associated with SNHL. 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, initial descriptions of the hearing improvement observed largely were believed to be minimal. 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. 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%. Interestingly, MWS may also comprise neurologic sequelae, including migraine, despite a negative magnetic resonance imaging; symptoms were controlled with IL-1 antagonism. 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 amloid deposits noted on kidney biopsy. Additionally, similar to Cogan disease, keratitis has been reported in MWS. 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. 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 SNHL will continue to grow. Multigian organ 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 immunemediated hearing losses.

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