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## The Attending Physician

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# IL-1 $\beta$ inhibition in autoimmune inner ear disease: can you hear me now?

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**Clinical vignette:** A 51-year-old man with right-sided sudden hearing loss presents to the otology clinic. He has a 4-year history of episodic vertigo of several hours' duration and fluctuating, progressive sensorineural hearing loss in his left ear. The vertigo attacks have not occurred for the last 18 months, and the left ear hearing is consistently poor. The patient's right ear hearing has dropped in the last 36 hours. MRI imaging of brain and temporal bone are normal. A 2-week "burst and taper" of oral prednisone is administered with no effect. Over the next 3 months, serial audiograms show rapidly progressive loss of threshold and word recognition scores on the right side. A trial of high-dose prednisone (60 mg/d for 30 days) results in full recovery of the right ear hearing and substantial improvement in the left ear. As the prednisone dose is slowly tapered over several months, the hearing drops again.

The patient above is likely suffering from autoimmune inner ear disease (AIED), a rare form of sensorineural hearing loss (SNHL). In 1979, McCabe provided the first clinical evidence that SNHL could have an autoimmune component (1), supporting the hypothesis put forth by Lehnhardt (2). Despite multiple confirmatory reports that have refined the clinical characterization of AIED, the pathogenesis of this very uncommon condition remains vague and controversial, in large part because there are no universally accepted diagnostic criteria or tests. A loose consensus has gradually arisen that AIED presents as an idiopathic, rapidly progressive, bilateral SNHL. AIED patients exhibit a loss of hearing that occurs over a period of weeks to months, too slow to be considered "sudden" SNHL and too fast to be classified as age-related or other genetically determined degenerative SNHL. Serial audiometry dem-

onstrates progression, which is usually monotonic but may fluctuate. Typically the ears progress asynchronously, often years apart. In many cases, deafness in the first ear may be congenital or the result of some identifiable cause prior to rapid hearing loss in the second ear, raising the possibility of AIED. This rapidly progressive asynchronous hearing loss alone is considered sufficient by some to make an AIED diagnosis, whereas others require evidence of steroid responsiveness.

## Current therapies

A classification scheme put forth by Harris et al. defines type 1 AIED as an idiopathic, rapidly progressive, bilateral SNHL with no evidence of other systemic autoimmune or inflammatory disease (Table 1 and ref. 3). A recent retrospective of 47 AIED cases by Matsuoka and Harris provides an excellent summary of the clinical epidemiology (4). In contrast to many sys-

temic autoimmune diseases, type 1 AIED equally affects males and females. Type 1 AIED onset typically occurs in the mid-50s and seems to be far more common in white (non-Hispanic) populations than in other racial/ethnic groups. Moreover, all type 1 AIED patients in the Matsuoka and Harris cohort exhibited aural pressure and tinnitus. Approximately 15% experienced vestibular symptoms of vertigo, disequilibrium, or dizziness.

Audiometric diagnosis of AIED typically consists of an auditory pure tone threshold shift of at least 15 dB at 1 test frequency or 10 dB at 2 or more consecutive test frequencies, or a greater than 12% drop in word recognition within a 3-month period. Often a single month-to-month comparison does not meet these criteria, but comparison of monthly audiograms over a 3-month span will clearly demonstrate progressive hearing loss. Unlike idiopathic sudden SNHL, which is an otologic emergency and has only a 2- to 4-week window for successful corticosteroid treatment (5), AIED appears to be steroid responsive for weeks to months. Unfortunately, once AIED hearing loss stabilizes, corticosteroids appear to no longer be effective (S.D. Rauch, unpublished observations).

Currently, the cornerstone of AIED therapy is corticosteroids. Typically, patients are given a therapeutic trial of oral prednisone, which is administered for 30 days, and hearing is reassessed. If there is a steroid response, patients are slowly tapered off of the corticosteroid. Each month, hearing is tested to confirm stability or improvement before further lowering the dose. Once the dose reaches 10 mg/d, this dose is continued for 3 months before the final taper to discontinue the medication; therefore, treatment duration is 6–12 months. If a patient exhibits hearing loss during any month of treatment, the current dose may be held for an additional month to see if the hearing will rise again. Alternatively, the dose can be bumped

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**Table 1. Harris AIED classification**

| Type   | Features  |
|--|---|
| 1: Organ-specific (ear)  | Rapidly progressive bilateral SNHL<br>All ages, although middle age most common<br>No other clinical evidence of autoimmune disease<br>Negative serology as evaluated by antinuclear antibody, erythrocyte sedimentation rate, rheumatoid factor, and C1q binding assay<br>>50% of patients respond to high-dose corticosteroids  |
| 2: Rapidly progressive bilateral SNHL with systemic autoimmune disease   | Rapidly progressive bilateral SNHL<br>Other autoimmune condition present, such as systemic lupus erythematosus, ulcerative colitis, polyarteritis nodosa, vasculitis, rheumatoid arthritis, and Sjögren's disease<br>Hearing loss often worse with flare-up of autoimmune condition<br>Serologic studies positive in accordance with systemic autoimmune disease<br>Steroid responsive, might be managed with targeted therapies for underlying illness |
| 3: Immune-mediated Meniere's disease   | Bilateral fluctuating SNHL with predominant episodic vestibular symptoms<br>Subset of patients with contralateral delayed endolymphatic hydrops or recent instability of better hearing ear in a patient with burned out Meniere's disease<br>Steroid responsive, might require long-term immunosuppression due to relapses   |
| 4: Rapidly progressive bilateral SNHL with associated inflammatory disease, such as chronic otitis media, Lyme disease, and otosyphilis            | Evidence of profound drop in hearing with longstanding chronic otitis media<br>Might show inflammation and perforations of tympanic membrane<br>Hearing loss progresses despite treatment of the infectious agent<br>Serological tests might be positive for underlying disease, patients should be evaluated for granulomatous disease and vasculitis by biopsy of tissue available<br>Steroid responsive, might require long-term immunosuppression   |
| 5: Immune-mediated SNHL with other discrete organ system disease, such as Cogan's syndrome, Wegener's granulomatosis, and relapsing polychondritis | Serologic tests may be positive in accordance with associated disease<br>Initially responsive to high-dose steroid, but tends to become resistant over time and with each relapse   |
| 6: Nonimmune rapidly progressive SNHL (ototoxic or paraneoplastic syndrome)  | Young to elderly patients with idiopathic rapidly progressive SNHL leading to deafness<br>Severe ear pain, pressure, tinnitus, and some imbalance<br>Negative serology<br>Inciting event common; drug-related (e.g., oxycodone), paraneoplastic syndrome<br>No response to corticosteroids or antiviral treatment   |

As described by Harris et al. (3).

back up until hearing stabilizes. Treatment with a total duration of less than 6 months is associated with a 100% relapse rate.

There are 3 possible outcomes for steroid-responsive AIED patients, the least likely of which is a successful taper with no further hearing problems. Most commonly, patients are successfully tapered off corticosteroids, but relapse or exhibit gradual, progressive hearing loss over the years. Some patients will have an outcome that falls between these extremes. These patients are considered to be steroid dependent, meaning that their hearing is stable while on steroids, but declines whenever the dose gets too low. In this patient subset, there is considerable inter-subject variability in the threshold prednisone dose required to maintain hearing stability. In steroid-dependent cases, it is often possible to introduce another immunomodulatory drug like a TNF- $\alpha$  inhibitor,

such as etanercept, infliximab, or adalimumab, and then successfully withdraw the corticosteroid. In some cases, the TNF- $\alpha$  inhibitor can be successfully withdrawn. Older and better-tolerated steroid-sparing agents, like methotrexate, have been evaluated for this purpose, but have been unsuccessful (6). For patients unresponsive to the initial 30-day prednisone trial, no other effective treatments are available.

### Knowledge gap

It is not clear exactly how the immune system damages the inner ear. It has long been thought that the inner ear is an immunologically privileged site protected from systemic immune system by a "blood-labyrinth barrier," akin to brain and blood-brain barrier; however, this notion has been disproven. Animal models have shown that systematic immunization with inner ear antigens produces inner ear dysfunction

(7, 8). Furthermore, a circulating antibody was identified in AIED patients that is immunoreactive with a 68-kDa inner ear antigen (9), which is likely HSP70 (10, 11). Efforts to assay anti-HSP70 antibodies as a clinical diagnosis and monitoring tool for AIED were initially hopeful; however, more recent analysis revealed that the sensitivity and specificity of this test is too low to be of clinical value (4). Multiple groups have identified circulating antibodies that target an inner ear protein found in supporting cells of the organ of Corti within the cochlea (12, 13) in 30%–40% of AIED patients. The antigen was eventually identified as the transmembrane protein choline transporter-like protein 2 (CTL2). A clinical correlation between the presence of anti-CTL2 antibodies and steroid responsiveness appeared robust in a small cohort of subjects, but no assay has been made available for clinical use.

## Research advance

Previously, Vambutas and colleagues collected inner ear perilymph samples during cochlear implantation in patients with profound deafness from end-stage AIED and used this perilymph to stimulate autologous peripheral blood monocytes (PBMCs). Compared with perilymph from control cochlear implant patients, perilymph from individuals with AIED induced the expression of interleukin-1 type II decoy receptor (IL-1R2) in PBMCs (14). Subsequent studies of PBMCs revealed increased IL-1 $\beta$  expression in steroid-resistant versus steroid-responsive AIED patients. Furthermore, the glucocorticoid dexamethasone was unable to prevent IL-1 $\beta$  release, but the IL-1 receptor antagonist anakinra effectively did (15). These observations shed new light on possible mechanisms of immunologic damage in AIED as well as offer a potential novel treatment with anakinra or other IL-1 $\beta$  inhibitors or receptor antagonists.

In this issue of the *JCI*, Vambutas et al. present results of an open-label, single-arm, phase I/II pilot study of anakinra for AIED patients that are unresponsive to corticosteroids (16). Of patients that completed an 84-day treatment, 7 of 10 showed at least a transient hearing improvement while receiving anakinra. Some of the subjects, deemed treatment responders, went on to exhibit a drop in hearing despite continuation of treatment. In each of these fluctuating cases, plasma IL-1 $\beta$  levels vacillated up and down in concordance with hearing. While the study by Vambutas and colleagues only evaluated a very small cohort, and numerous details in the methodology are debatable, it provides

a potential treatment with demonstrated efficacy in corticosteroid nonresponders. Moreover, the correlation of hearing levels and plasma IL-1 $\beta$  levels corroborates earlier work that supports a role for cytokines in the etiopathogenesis of AIED.

## Recommendations

While AIED is a very rare condition, it represents one of the few examples of potentially reversible SNHL. For that reason, and because of the insights that may be gained from pursuing treatment of AIED and other SNHLs with cytokine modulators, the present report by Vambutas et al. (16) is exciting. Additionally, this report indicates that IL-1 $\beta$  has potential as a clinical marker to evaluate treatment response and predict outcome. Further prospective, randomized, multicenter clinical trials are now needed to confirm and extend these preliminary results.

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