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 demonstrates 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 systemic 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

**Related Article: p. 4115**

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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 intersubject 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-α inhibitor, such as etanercept, infliximab, or adalimumab, and then successfully withdraw the corticosteroid. In some cases, the TNF-α 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 systematic 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 (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.
IL-1β is a potential novel treatment with demonstrated efficacy in corticosteroid nonresponders. Moreover, the correlation of hearing levels and plasma IL-1β 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-1β 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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