Introduction

Autoimmune inner ear disease (AIED) is a relatively new etiologic mechanism of sudden or rapidly progressive hearing loss which has been added to the previously accepted triad of viral, vascular, and membrane rupture. This condition implies that inner ear proteins are recognized immunologically as foreign or non-self. It has been proposed that this occurs as a primary autoimmune phenomenon, or as a result of the exposure of an immune privileged antigen through trauma or an inflammatory process. Because these inner ear antigens are not yet known, some clinicians still doubt the existence of AIED. No one can deny, however, that a large percentage of patients with suspected AIED, who were once thought to have progressive, irreversible hearing loss, will benefit from treatment with immunosuppressive drugs if they are started early in the disease course.

McCabe first described AIED in 1979. He reported on eighteen patients with bilateral rapidly progressive sensorineural hearing loss (SNHL) for which no identifiable cause could be found. Evidence of autoimmunity in these patients included a positive lymphocyte inhibition test. In this test, patient’s serum was combined with antigens derived from the membranous labyrinth of patients who had undergone translabyrinthine resection of acoustic tumors. All patients' sera reacted to some antigens while controls did not. Additional evidence of autoimmune etiology was indicated by the fact that patients had substantial hearing improvement with steroid treatment. Furthermore, histopathologic examination of one patient’s temporal bone revealed vasculitis. McCabe proposed that the diagnosis of AIED be based on positive immune laboratory tests and beneficial treatment response. He also further characterized AIED from other causes of sudden sensorineural hearing loss (SSNHL) in that hearing loss is typically bilateral and asymmetric, progressive of several months with episodes of improvement, and associated with vestibular symptoms.

Since McCabe’s first description AIED, support for the existence of this disease has grown as a result of extensive basic science research. Animal studies have proven that the inner ear does in fact have immunity and is not an immune privileged site as once thought. The
endolymphatic sac has been shown to contain immunocompetent cells even in a normal resting state and seems to be the inner ear site where antigen processing is carried out. It serves to protect the rest of the inner ear from foreign substances and infectious agents. Experiments have shown brisk immune mediated inflammatory responses in the endolymphatic sac after direct inoculation with viral components with preservation of hearing and balance. The cochlea on the other hand is devoid of immune cells. It has been shown, however, that when an antigen is injected into the scala tympani, it will eventually diffuse into the endolymphatic sac where it may potentially illicit an immune response.

Experimental evidence has also supported the existence of AIED. It has been found that animals immunized with inner ear proteins can produce modest, transient hearing loss and cochlear inflammation (Orozco et al., 1990). Despite this evidence from animal models, the existence of a specific autoimmunity within the inner ear remains controversial. Although candidate antigens including a 68 kDa protein, type II collagen, and several other antigens have been proposed, a single target antigen of autoimmunity has been elusive. This is not surprising considering the fact that the inner ear is comprised of thousands of different proteins, many of which are intimately involved with auditory and vestibular functions.

Histopathology consistent with autoimmune disease is one of the criteria used to establish an autoimmune etiology. This is of course impossible to obtain with respect to the inner ear of patients with suspected AIED. A few temporal bones of patients with suspected AIED have been examined postmortem and have shown osteoneogenesis consistent with past inflammation, but the histopathology was of course not concurrent with the onset of disease.

Response to immunosuppression has often been cited as evidence for an autoimmune process in the inner ear. Through animal studies it appears that immuno-suppression can reduce immune-mediated SNHL. Animals pretreated with cyclophosphamide followed by viral challenge of the inner ear have been shown to have decreased incidence and severity of hearing loss measured by eighth nerve compound action potentials (Darmstadt et al.). We know of course, that drugs such as steroids and cytotoxic agents are not specific to immunity. These drugs can, by reducing the number of circulating leukocytes, reduce inflammation due to a number of causes.

Ultimately, we still lack the definitive evidence that most scientists and immunologists demand in order to conclude that autoimmunity does in fact occur in organ-specific manner in the inner ear.

**Etiology of SSNHL**

The etiology of SSNHL can be broken down into broad categories: (1) viral and infectious, (2) autoimmune, (3) labyrinthe membrane rupture/traumatic, (4) vascular, (5) neurologic, and (6) Neoplastic. There are multiple conditions within each of these categories that have been associated with SSNHL. The following is a partial list of reported causes of SSNHL:

**Infectious**  
Meningococcal meningitis  
Herpesvirus (simplex, zoster, varicella, cytomegalovirus)
Mumps
Human immunodeficiency virus
Lassa fever
Mycoplasma
Cryptococcal meningitis
Toxoplasmosis
Syphilis
Rubeola
Rubella
Human spumaretrovirus

**Autoimmune**

Autoimmune inner ear disease (AIED)
Ulcerative colitis
Relapsing polychondritis
Lupus erythematosus
Polyarteritis nodosa
Cogan’s syndrome
Wegener’s granulomatosis

**Traumatic**

Perilymph fistula
Inner ear decompression sickness
Temporal bone fracture
Inner ear concussion
Otologic surgery (stapedectomy)
Surgical complication of nonotologic surgery

**Vascular**

Vascular disease/alteration of microcirculation
   Buerger’s disease
Vascular disease associated with mitochondriopathy
Vertebrobasilar insufficiency
Sickle cell disease
Cardiopulmonary bypass

**Neurologic**

Multiple sclerosis
Focal pontine ischemia
Migraine

**Neoplastic**

Acoustic neuroma
Leukemia
Myeloma
Metastasis to internal auditory canal
Meningeal carcinomatosis
Autoimmune

In addition to the proposed organ-specific AIED, autoimmune hearing loss may also be associated with or part of systemic autoimmune diseases such as Cogan's syndrome, Wegener’s granulomatosis, polyarteritis nodosa, temporal arteritis, Buerger’s disease (thromboangitis obliterans), and systemic lupus erythematosus. The pathogenesis of immune-mediated sensorineural deafness and vestibular dysfunction are unclear, but are presumed to include: vasculitis of vessels supplying the inner ear, auto-antibodies directed against inner ear antigenic epitopes, or cross-reacting antibodies.

Cogan's syndrome (CS) is an autoimmune disease of the cornea and vestibuloauditory apparatus that was first described by Cogan, an ophthalmologist, in the 1940s. It occurs primarily in young adults (average age of onset 22-29 years) and typically presents with interstitial keratitis (IK) and Meniere’s-like attacks of vertigo, ataxia, tinnitus, nausea, vomiting, and hearing loss which develop within several months of each other. CS may also be associated with other systemic manifestations of the inflammatory process such as Takayasu's-like or medium-sized vessel vasculitis. Approximately 10% of patients develop aortitis within weeks to years after the onset. Hearing fluctuation in CS coincides with disease exacerbations and remissions. Its course often culminates in deafness. One series reported that 12 out of 18 patients (67%) developed bilateral deafness.

The cause of CS is unknown. Microbial etiology has been suggested by some as a URI precedes nearly 40% of patients who present with this disease. Clinical parallels between syphilis and CS have led some to believe that CS may be caused by Borrelia burgdorferi. However, evidence so far has been inconclusive. There have also been links to Chlamydia species with CS and is an area of ongoing investigation. Temporal bone histopathologic studies done at autopsy of patients with CS are characterized by chronic inflammation including: infiltration of the spiral ligament with lymphocytes and plasma cells, endolymphatic hydrops, degenerative changes in the organ of Corti, and demyelination and atrophy of the vestibular and cochlear branches of the eight cranial nerve.

There is no criteria currently established for the diagnosis of CS. The general thinking is that the diagnosis requires clinical signs of both eye and inner ear inflammation. Work-up should include an audiogram and laboratory tests including CBC, ESR, and RPR. Imaging including MRI and/or CT should be done primarily to rule out cerebropontine angle tumors and other disorders. MRI may show enhancement of vestibular and cochlear structures with gadolinium.

History and Physical

Evaluation and management of rapidly progress or SSNHL should be considered medically urgent, if not an emergency. The primary goal is to rule out any treatable causes and begin treatment early in the course of the disease.

Diagnostic evaluation of the patient with sudden hearing loss begins with a thorough history and physical exam. Details of the circumstances surrounding the hearing loss and the time course of its onset should be elicited. Associated symptoms, such as tinnitus, vertigo or
dizziness, and aural fullness should also be asked about. Clinical experience has shown that about one-third of patients note their hearing loss upon first awakening in the morning, and that about one-half of cases will have associated vertigo. Patients should also be questioned about previous otologic surgery, ototoxic drug use, and previous or concurrent viral or upper respiratory tract infections. Any history of trauma, straining, diving, flying, and intense noise exposure should be noted. Past medical history of other diseases associated with sudden hearing loss should also be obtained such as diabetes, autoimmune disorders, malignancies, neurologic conditions (multiple sclerosis), and hypercoagulable states. African-Americans should be asked about sickle cell disease.

A complete head and neck exam should be performed on all patients with sudden hearing loss. More often than not, the exam will be unremarkable, however, any processes such as middle ear effusions, infections, cholesteatoma, and cerumen impaction should be excluded. A thorough neurological exam including Weber and Rinne, cranial nerves, and cerebellar and vestibular testing should be performed.

Although AIED is categorized by most sources as cause of SSNHL, the clinical picture of AIED differs from other causes of SSNHL in that it usually consists of rapidly progressive (over weeks to months) rather than sudden (hours to days), bilateral, asymmetric, sensorineural hearing loss. The hearing loss tends to wax and wane with disease activity. Systemic manifestations are usually absent which distinguishes it from other known autoimmune disorders. One series found that less than 30% of patients with rapidly progressive SNHL had an associated systemic autoimmune disorder. Approximately 50% of patients will complain of dizziness. Episodic light-headedness or mild ataxia is more common than true vertigo. Also, these episodes occur multiple times daily during active disease as opposed to two or three discrete episodes per week, as is seen in Meniere’s disease. Occasionally symptoms of pressure and tinnitus can occur. The symptoms often progress over weeks or months but can also present as sudden hearing loss or protracted disease over many years. Most patients present with bilateral disease, and when dizziness is present, vestibular testing usually reveals bilateral reduced response. AIED has a slight predominance in middle-aged females, but can occur in both sexes and can begin in childhood.

**Diagnosis**

An audiogram (pure tone, speech, tympanometry, including stapedial reflex testing) should be performed on all patients with sudden hearing loss. The audiogram is the foundation of the diagnosis and provides prognostic information. Serial testing provides documentation of the progression or resolution of the hearing loss and response to treatment. In addition it may help exclude patients with secondary gain or with pseudohypacusis.

The following is a list of laboratory studies that can be ordered. Initial screening tests should be directed based on history and suspected conditions.

1) Complete blood count (CBC)
2) Erythrocyte sedimentation rate (ESR)
3) C-reactive protein (CRP)
4) Glucose
5) Cholesterol/triglycerides
6) T3, T4, TSH
7) VDRL, RTA-ABS (MHA-TP)
8) HIV
9) Lyme titer
10) Antigen-specific cellular immune tests
   Lymphocyte transformation test (LTT)
   Western blot immunoassay

Magnetic resonance imaging (MRI) is recommended by the majority of authors for patients with asymmetric hearing loss. In one survey of 79 otolaryngologists, 38% would order imaging on the patient’s initial visit. MRI is useful in evaluating for acoustic tumors, multiple sclerosis and cerebrovascular accidents. There are some proponents of following these patients and imaging only if asymmetric hearing persists. However, Berg et al., in a series of acoustic neuromas showed that 13% presented with sudden hearing loss, and of these 23% recovered auditory function.

The diagnosis of AIED by most clinicians is based on the presence of bilateral progressive sensorineural hearing loss and response to immunosuppressive therapy. To this date, proof of a causal relationship of autoimmunity and sudden or rapidly progressive hearing loss has not been definitively established. Without definitive evidence of the existence of AIED, diagnostic and treatment studies are currently based on a presumptive diagnosis.

Hughes proposes that the two most clinically helpful tests for diagnosing AIED are the lymphocyte transformation test (LTT) and the Western blot immunoassay. These are both antigen-specific immune tests. The sensitivity and specificity for LTT are estimated to be 50-80% and 93% respectively with positive predictive values ranging from 56-73% depending on the disease prevalence in the tested population. When applied to high risk populations (patients with bilateral rapidly-progressive SNHL), the Western blot has a sensitivity of 88%, a specificity of 80%, and an overall positive predictive value of 92%. For these tests to work, high levels of circulating autoimmune antibodies are ideal. Because the disease waxes and wanes, testing should be performed during periods of disease activity and before treatment is initiated.

Currently, tests for AIED are not routinely used except at certain centers (Cleveland Clinic and the Massachusetts Eye and Ear Infirmary) and in experimental trials. The major drawback to these studies is the lack of availability. If testing is desired, samples of whole blood from patients can be mailed to the Cleveland Clinic Foundation Regional Laboratory by overnight carrier for LTT. The test costs $120.00 and results take approximately seven days.

The best theoretical test for AIED would be a test for a marker specific for AIED. Attempts have been made in this area and are promising. In 1990, Harris and colleagues published the results of studies which discovered, using Western blot, an anti-68 kDa autoantibody in the sera of patients with rapidly progressive SNHL. Since then, other studies have confirmed these findings in humans (Moscicki, 1990) and in autoimmunized animals (Orozco, 1990 and Harris, 1990). Interesting, despite the species of animals used, analysis of sera from hearing-impaired animals by Western blot revealed an antibody against an inner-ear antigenic epitope with a molecular weight of approximately 68 kDa.
Overall 22% to 89% of sera of patients with rapidly progressive SNHL will contain this antibody. Moscicki emphasizes the importance of testing patients during disease activity. In his series, 89% of patients with active disease tested positive for anti-68 kDa antibodies versus 0% in patients with inactive disease. Harris has reported a 94% specificity for test correlating results with responsiveness to therapy and disease activity. Studies by Billings and Harris are now searching for the specific antigen involved in AIED. So far they have isolated a 68 kDa protein that is ubiquitous in the inner as well as other areas of the body, and have recently reported evidence that links the 68kDa antigen with heat shock protein 70 (hsp 70), a highly inducible stress protein. Further research is needed in this area to determine the exact relationship of hsp 70 to AIED and whether it plays an important etiologic role or whether it is just a bi-product of the disease itself. Theories proposed are that (1) human hsp 70 may have a similar amino acid sequence to an infecting agent resulting in cross-reactivity or (2) that there may be a hsp 70 specific to the inner ear that is seen as foreign when it is over-expressed during times of chronic inflammation from an outside agent. Support for this theory has been shown by Gong and Yan (2002). They showed that guinea pigs immunized with homologous crude inner ear antigen (CIEAg) had significantly increased expression of hsp70 compared to controls. Trune et al. (1998) were unable to induce hearing loss with hsp 70 in guinea pigs. This same finding held true for Harris who immunized mice with the protein and found no hearing loss.

In addition to the 68 kDa/hsp 70, multiple other candidate antigens have been proposed such as type II collagen (Yoo et al., 1982), beta tubulin (Connolly et al., 1997), 30 kDa protein, and c Raf.

**Treatment**

Treatment for AIED is controversial and widely varied from practitioner to practitioner. This is largely due to the lack of double-blind, prospective clinical trials on the matter. The general consensus is that steroids are effective and should be used. Most sources recommend prednisone 1mg/kg/day for 4 weeks followed by a slow taper if the patient responds. If the patient relapses on the taper, Harris recommends instituting high dose prednisone (up to 2mg/kg) and if continued recurrence occurs with tapering, a cytotoxic agent such as methotrexate (MTX) or cyclophosphamide (Cytoxan) should be instituted. Most sources recommend starting MTX at a dosage of 7.5-15 mg weekly with folic acid (as recommended by the FDA for treatment of rheumatoid arthritis). Harris recommends a higher dose of MTX: 15-25mg. If MTX is used, the steroids should be continued after starting the MTX as it takes one to two months for the prednisone sparing affects of MTX to begin. Most physicians begin with MTX as it has fewer side-effects than Cytoxan. If both prednisone and MTX are ineffective, Cytoxan should be used (100mg po bid).

Other authors such as McCabe are more in favor of starting cytotoxic drugs at the onset of the illness. He believes that Cytoxan is the preferred treatment of AIED rather than steroids because in his series he has found a higher response rate to this drug. He believes that because the diagnosis of AIED is based partially on response to therapy, fewer patients with this diagnosis would be missed.

It is important to monitor for side effects of both MTX and Cytoxan with routine monitoring of complete blood counts, platelets, LFTs, UA, and electrolytes. Those on Cytoxan
should keep well-hydrated to prevent hemorrhagic cystitis. If possible, a physician (Rheumatologist) experienced in the use of these cytotoxic drugs should be consulted to assist with dosage adjustments and managing side effects.

Data on hearing response to therapy is relatively lacking with the majority of studies being retrospective. Sismanis (1997) looked at treatment with MTX and reported that 69.6% had improvement in hearing and 80% had improvement of vestibular symptoms. He supported the use of MTX particularly for long term use because of its low complication rate compared to cyclophosphamide and steroids.

In a prospective trial, Matteson (2001) treated patients with 3 weeks of high dose prednisone taper and found a 72% rate of partial hearing improvement. He included patients with bilateral Meniere’s disease and Cogan’s disease.

Moscicki (1994) emphasizes the utility of the Western blot for detection of anti-68 kDa antibodies to determine which patients will respond to treatment. In his series of 75% of patients with a positive test responded to treatment vs. 18% with a negative test.

Recently, Harris et. al (2003) looked at the affect of MTX versus placebo in maintaining the hearing improvement in patients responsive to prednisone. This was a randomized, double blinded, placebo controlled trial. He found a 57% rate of hearing improvement over all with initial treatment with prednisone. No difference was found however in hearing preservation after steroid treatment between the two groups. They concluded that MTX should no be used to maintain hearing improvement achieved with prednisone in patients with AIED.

Lasak et. al (2001) retrospectively looked at patient with presumed AIED and Western blot assay positive for a 68 kDa inner ear antigen who were treated with steroid alone or steroids plus cytotoxic agents (methotrexate, cyclophosphamide, and azathioprine). They found an over all improvement in hearing of 59%. The steroid-only responders tended to demonstrate a greater improvement in pure tone averages (14.8 vs 4.5 dB), while the cytotoxic-agent responders had a significantly greater improvement in speech discrimination (26.2 vs 6.9%). They concluded that cytotoxic medications improve discrimination even in some patients who are steroid non-responders.

Plasmapheresis (PMP) has also been proposed as a treatment for AIED (Luetje, 1989). The mechanism of action of plasma exchange involves the removal of circulating antibodies, antigens, and immune complexes and may enhance the effects of immunosuppressive agents. Luetje (1997) reported on his experience treating 21 patients with rapidly progressive SNHL with PMP. Several of his patients had dramatic improvement in hearing after treatment. Some were able to be taken off immunosuppressive agents and remained asymptomatic off of them. Luetje confesses that data from his series is confounded by several factors including retrospective analysis and concurrent use of immunosuppressive agents in some patients while not in others (those who could not tolerate them). Further research into this area is probably warranted. If hearing loss is truly autoimmune in some patients, it would make sense to see benefits with PMP. Perhaps effects on patients with positive screening for specific antigens such as hsp 70 would be more dramatic as is seen with steroid treatment in these patients.
It is important to keep in mind that some patients with AIED will not improve on treatment or progress to bilateral profound hearing loss. These patients are excellent candidates for cochlear implantation or other cochlear prosthetic devices and should be counseled about such options depending on the severity of their hearing loss.

**Prognosis**

The natural history of AIED is not known, however, clinical experience reveals that the disease waxes and wanes. Published series looking at patients with rapidly progressive SNHL and SSNHL report spontaneous recovery rates ranging from 47% to 63%. These reviews combined patients with partial and complete recovery and patients with all audiogram types. Four variables have been shown to affect recovery from SSNHL: (1) time since onset, (2) audiogram type, (3) vertigo, and (4) age. In 1984, Byl published a prospective study conducted over 8 years that evaluated 225 patients with SSNHL. Factors evaluated included age, tinnitus, vertigo, audiogram pattern, time elapsed from onset of hearing loss to initial visit, and ESR level with respect to recovery. His findings were as follows:

1) **Time since onset** - His study confirmed that the sooner the patient was seen and therapy initiated, the better the recovery. 56% of patients presenting within the first seven days of their hearing loss recovered compared to 27% who presented thirty days or later. He noted that there is some self-selection bias whereby those that recover rapidly do not seek medical aid.

2) **Age** - The average age for those recovering totally was 41.8 years. Those under 15 years and over 60 years had significantly poorer recovery rates.

3) **Vertigo** - Patients with severe vertigo had significantly worse outcomes than patients with no symptoms of vertigo. 29% of patients with vertigo recovered compared to 55% with no vertigo.

4) **Audiogram** - Patients with profound hearing loss had significantly decreased recovery rates compared to all other groups (22% with complete recovery).

Other series have shown that patients with midfrequency hearing loss, particularly when hearing at 4000kHz was worse than 8000kHz, have an excellent prognosis. 100% of patients in Laird's series in 1983 recovered completely. The majority of studies confirm the findings that profound hearing loss is a poor prognostic sign indicating more severe injury.

**Conclusion**

Rapidly progressive or sudden hearing loss no matter what the cause is a medical condition which can be particularly devastating to patients and frustrating for the otolaryngologist to diagnose and treat. Despite extensive investigation, only minimal data has been generated in the past thirty years to improve our understanding of the etiology and appropriate treatment of this disease. Most authorities agree that all patients should undergo audiometry, and imaging with MRI for those patients with asymmetric hearing loss, however the etiology for the majority of patients will go undiagnosed. Treatment is more controversial.
Steroids have been shown to significantly improve hearing recovery in patients with moderate to severe hearing loss and seem to be favored for the treatment of autoimmune and idiopathic forms of SSNHL. The remainder of proposed treatments for this disease are based, for the most part, on theory and will require further investigation to confirm or disprove their efficacy.

Development of future treatments for AIED will be dependent on the understanding of the exact immunologic events that occur in patients with this disease. Current ongoing investigations are looking at the role of helper T lymphocytes in experimental models of AIED. In particular, scientists are looking at the role of Th2 lymphocytes which appear to be capable of inducing a state of immunological unresponsiveness. By understanding the pathophysiological role of gene products of these cells in autoimmune hearing loss or, more importantly, by delineating their potential role in the maintenance of “tolerance” of self antigens, novel immunotherapeutic strategies may evolve.

References


Lasak, JM et. al: Autoimmune inner ear disease: steroid and cytotoxic drug therapy. *Ear Nose and Throat J.* 2001;80(11:808-822


