GUEST EDITORIAL

UNDERSTANDING AUTOIMMUNE EAR DISEASE
A POTENTIALLY TREATABLE CAUSE OF DEAFNESS

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INTRODUCTION

Sensorineural hearing loss (SNHL) is a common finding with an exhaustive list of etiologies. Rapidly progressive sensorineural hearing loss is quite distressing to patients as they are abruptly required to function with a reduced level of sensation of their environment. Autoimmune inner ear disease (AIED) is a rare diagnosis and frequently omitted from the differential diagnosis when evaluating patients with rapidly progressive sensorineural hearing loss. This is unfortunate as AIED represents a potentially treatable cause of hearing loss and vestibular symptoms. The goal of this discussion is to acquaint the reader with clinical presentation, diagnosis and treatment of AIED.

Background.

Lenhardt in 1958 hypothesized that anticochlear antibodies were a cause of bilateral SNHL but had no evidence to support this contention. In 1979 McCabe reported a series of patients with bilateral asymmetric SNHL that progressed over weeks to months and evidence of vestibular deficiencies. All patients had a response to immunosuppressive medications. This led him to describe a new syndrome of autoimmune sensorineural hearing loss. Since this original description, much investigation has further consolidated the existence of such a disease and brought forth diagnostic tests that aid in making the diagnosis. Harris and Sharp in 1990 reported the detection of a specific autoantibody with a molecular weight of 68-kilo Daltons (kDa) using Western blot analysis in 35% of their patients.

Immune functions of the Inner Ear.

Traditional thought was that the inner ear existed as an immunoprivileged site as the brain and is protected from immune function. This is partly due to the existence of blood brain and blood labyrinthine barrier. In the inner ear, the blood labyrinthine barrier serves to maintain the ionic characteristics of the cochlear fluids. Like the CSF, perilymph contains immunoglobulins at a concentration of 1/1000th of that in the serum. Immunoglobulin G (IgG) is the predominant antibody while IgM and IgA are present in lesser concentration. The inner ear shows a greater tendency to be immunoresponsive than the brain. Harris et al. found that antigen presented to the inner ear evoked an immune response equal to immunization via a peritoneal route while exceeding the response elicited by immunization through the middle ear. It is therefore evident that antigen within the cochlea readily gains access to the systemic circulation.

The endolymphatic sac (ELS) plays a significant role in the inner ear immune response. The sac contains a resident population of lymphocytes. It has been shown that the immune response within the ear may be significantly reduced and cochlear damage decreased with the destruction of the ELS or the duct. The lymphocytes responding to the antigenic stimulation in the inner ear enter from the systemic circulation, apparently via the spiral modiolar vein. The endothelial cells of the spiral modiolar vein undergo activation and express intracellular adhesion molecule during the secondary immune response. All four types of immune reactions described by Gell and Coombs have been hypothesized to contribute to inner ear disease. Type I immune reactions are mediated by IgE and characterized by the activation of sensitized mast cells with the release of histamine and other vasoactive substances. The type I immune response has been hypothesized as a cause of disruption of ionic transport within the inner ear due to histamine induced vasodilatation, resulting in endolymphatic hydrops.

Type II reactions occur when antibodies directed against a specific antigen within tissues elicit the activation of complement. The antigen can be either from an exogenous source (virus or drug) or may be directed at an endogenous source as in the case of anti DNA antibodies of systemic lupus erythematosus (SLE) or the anti basement membrane antibodies that cause renal involvement in Good Pasture’s syndrome. Evidence is growing that Type II immunity is a cause of inner ear disease. It has been shown that 34% of sera isolated from Meniere’s patients reacts with preparations from the inner ear of guinea pigs implying a

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specific antibody directed toward an inner ear antigen. In addition, patients with Meniere’s disease have been shown to have greater reactivity with type II collagen than controls.

Type III reactions are the result of the deposition of intermediate sized immune complexes in the microcirculation. The deposition of these biologically active immune complexes induces vascular injury with subsequent injury to the labyrinthine structures. Consistent with this theory has been the demonstration of deposition of immunoglobulin around an apparently occluded blood vessel as shown by immunofluorescence of the ELS in patients with Meniere’s disease. In addition, Derebery et al. analyzed sera from 30 patients with Meniere’s disease. Ninety five percent of these patients demonstrated elevated levels of circulating immune complexes as compared with 20% of controls. Hearing loss and vestibular dysfunction has been demonstrated in diseases known to be mediated by systemic immune complexes including systemic lupus erythematosus (SLE) and Wegener’s granulomatosis (WG). These observations provide substantial evidence that Type III immune reactions play a role in some instances of inner ear pathology.

Type IV immune reactions are characterized by T cell mediated delayed hypersensitivity. Evidence supporting the role of Type IV reactions in inner ear disease is largely from laboratory testing. The lymphocyte transformation test measures the difference in proliferation of a patient’s lymphocytes when exposed to preparations of inner ear antigens as compared to the lack of this exposure. While lacking in sensitivity and specificity, it does indicate that some patients have evidence of an inner ear antigen specific cellular immune response. While the exact mechanism of injury in immune mediated ear disease are yet to be described, all types of immune responses have been hypothesized to cause labyrinthine damage, a large volume of information supports immune dysfunction as cause in at least some cases of SNHL.

Clinical Features and Diagnosis.
Autoimmune inner ear disease most commonly affects middle-aged women, much like other autoimmune diseases. The usual presentation is that of a progressive SNHL over weeks to months. The hearing typically fluctuates and progressively worsens. Dizziness and aural fullness are common. Classically, the hearing in one ear becomes poor while the other remains serviceable. The diagnosis is considered until there is a drop in hearing in the better hearing ear, prompting the clinician to consider an immune etiology and initiate steroid therapy. Vestibular function may be lost gradually so that acute symptoms do not occur, but patients may develop ataxia and unsteadiness more noticeable in darkness with bilateral vestibular hypofunction.

The diagnosis of AIED has been difficult to standardize and still largely relies on the clinical presentation. Laboratory tests that would allow the definitive diagnosis of AIED have been the area of interest. McCabe felt that the lymphocyte inhibition test offered a strong argument for autoimmune disease. More recently, the lymphocyte transformation test has been used to demonstrate cellular mediated autoimmune reaction to inner ear antigens. The test is performed by isolating lymphocytes from patients suspected of having AIED and exposing them to inner ear antigens. If the lymphocytes are sensitized to the antigens, the lymphocytes become active and release lymphokines. This is considered a positive test suggestive of a T cell mediated autoimmune response directed toward inner ear tissues. The specificity is estimated at 93% and sensitivity at 50-80% during the active phase of the disease. Other authors have reported the LTT against type II collagen as being more useful.

Perhaps the most promising definitive test for AIED is the Western blot immunoassay to 68kDa antibody. This test is performed by electrophoresing inner ear antigens onto a gel and incubating them for several hours with a dilute solution of the patient’s serum. Harris and colleagues found a specific anticochlear antibody reacting to an antigen in the inner ear in the molecular weight range of 62000-68000. Seventy five percent of the patients who tested positive responded to steroid therapy as compared to only 18% of those who tested negative.

Many laboratory tests have been used in the evaluation of SNHL. In an effort to better delineate the diagnostic value of a panel of laboratory tests, Hirose et al. examined the results of their testing in suspected cases of AIED. Their test battery included erythrocyte sedimentation rate, C-reactive protein, (CRP) antecardiolipin antibody (aCL), antineutrophil cytoplasmic antibody ANCA), microhemagglutinin assay for Treponema pallidum They found that the best test for predicting steroid responsiveness was the Western blot for hsp 70.
The differential diagnosis of the patient with rapidly progressive SNHL is rather extensive and includes AIED, Meniere's disease, recessive progressive hereditary deafness, vascular insufficiency, hypercoagulability syndrome as a result of antiphospholipid antibody, acoustic schwannoma and otosyphilis. As a general rule, the evaluation should be tailored to the clinical picture and the appropriate workup performed. This may include imaging if structural abnormalities or retrocochlear pathology is suggested by history, physical examination and audiogram. As research continues and a better understanding of AIED is attained, perhaps a standardized test panel will prove reliable and efficacious, but for the time being, ESR and Western blot assay for hsp 70 appear to be the most useful test in the diagnosis of AIED.

Treatment.
Patients with progressive SNHL that is believed to be due to AIED should be considered for immunosuppressive therapy. Steroids remain the foundation of therapy. Patients should be started on Prednisolone 1mg/kg day (60mg daily dose for adults). An initial therapeutic trial of 3-4 weeks may determine the response to therapy. Those who respond can be slowly tapered with the high doses reinstituted for relapses. A maintenance dose of 20mg every other day may be required for 3-6 months. Before starting such a regimen, the potential risks and side effects associated with high dose steroid therapy should be discussed in detail.

McCabe insists that cyclophosphamide is the cornerstone of therapy and advocates the institution of treatment in any patient in whom the disease is suspected. Cyclophosphamide is started in a dose of 60mg every 12 hours with prednisolone 30 mg every other day for 3 weeks. If the patient shows some response to this treatment, the therapy at the same doses is continued for 3 months. The potential complications of cyclophosphamide therapy include hemorrhagic cystitis, leukopenia, sterility and malignancy of the urinary tract. For this reason, patients should be followed closely and have surveillance of the white blood cell counts and urinalysis while on the treatment regimen.

Recently methotrexate has received attention as a possible therapeutic agent in AIED for success in the treatment of Rheumatoid arthritis. Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, thereby interfering with DNA synthesis, repair and replication. Sismanis et al demonstrated that 69.9% of 25 patients with immune mediated cochleovestibular diseases had hearing improvement and 80% of patients with vestibular symptoms had substantial improvement. Therapy was begun at 7.5mg per week and in most patients was increased to 12.5 mg per week. Eight patients had rather mild and reversible complications including nausea, oral ulcerations, transient rash and minimal alopecia. Further investigations are needed but methotrexate may prove to be an alternative to long-term high dose steroids.

Conclusion.
Autoimmune inner ear disease is a relatively newly described disease process of which little is known of the etiology, diagnosis and treatment. Clinicians should be aware of the presentation and diagnosis of the disease as it may represent a treatable cause of progressive deafness. While steroids are useful in many patients, some are unable to tolerate the doses and length of therapy required for benefit, while alternative therapies have the potential for serious complications. New medications and treatments are needed and are certain to be discovered as experience with the disease increases.

REFERENCES


