Autoimmune Inner Ear Disease: Diagnostic and Therapeutic Approaches in a Multidisciplinary Setting

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Abstract

Autoimmune Inner Ear Disease (AIED) is a clinical syndrome of uncertain pathogenesis. It is associated with bilateral rapidly progressive hearing loss. The hearing loss may be associated with vestibular symptoms. Autoimmunity has been proposed as the pathogenesis of this sort of hearing loss, although the mechanism of the disease is poorly understood. It is well accepted that the endolymphatic sac is an immunocompetent organ and circulating autoantibodies against inner ear antigens have been reported, as have viral antigens in the endolymph, although the sensitivity, specificity, and roles of those antibodies in a disease process are poorly defined.

We will describe the clinical aspects of the disease, the histopathology, the immunologic indicators, the types of presentation, both from the audiologic and vestibular point of view, clinical trials for treatment and the follow-up. One of our conclusions is that many of these patients respond favorably to the treatment Methotrexate.

Key Words: Autoimmune inner ear disease, Methotrexate, Sensorineural hearing loss, PET Scan

Abbreviations and Acronyms: AIED=Autoimmune Inner Ear Disease; SNHL=Sensorineural Hearing Loss; ESR=Erythrocyte sedimentation rate; HSP-70=Heat shock protein 70; PET Scan=Positron emission tomography; MTX=Methotrexate; FDG=18-fluoro-2-deoxyglucose; MRI=Magnetic resonance imaging; TNF=Tumor necrosis factor

Sumario:

La enfermedad autoinmune del oído interno (AIED) es un síndrome clínico de patogénesis incierta. Se asocia con un trastorno auditivo bilateral rápidamente progresivo. La hipoacusia puede asociarse con síntomas vestibulares. Se ha propuesto la autoinmunidad como la patogénesis de este tipo de trastorno auditivo, aunque el mecanismo de la enfermedad está pobremente entendido. Se acepta ampliamente que el saco endolinfático es un órgano inmunocompetente y se ha reportado la existencia de anticuerpos circulantes contra el oído interno. También se ha reportado la presencia de antígenos virales en la endolinfa, aunque la sensibilidad, especificidad y el papel de estos anticuerpos en el proceso de la enfermedad aún no ha sido bien definida.

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Describiremos los aspectos clínicos de la enfermedad, la histopatología, los indicadores inmunológicos, los tipos de presentación tanto desde el punto de vista audiológico como vestibular, los estudios clínicos para el tratamiento y el seguimiento. Una de nuestras conclusiones es que muchos de estos pacientes responden favorablemente al el tratamiento con Metotrexate.

**Palabras Clave:** Enfermedad auto-inmune del oído interno; metotrexate, hipoacusia sensorineural, Prueba de PET.

**Abreviaturas y Acronimos:**
- **AIED** = enfermedad auto-inmune del oído interno;
- **SNHL** = hipoacusia sensorineural;
- **ESR** = Tasa de eritrosedimentación;
- **HSP-70** = proteína 70 de choque térmico;
- **PET Scan** = tomografía de emisión de positrones;
- **MTX** = metotrexate;
- **FDG** = 18-fluoro-2-dexosiglucosa;
- **MRI** = imágenes por resonancia magnética;
- **TNF** = factor de necrosis de tumor.

**Autoimmune inner ear disease (AIED)** is a clinical syndrome of uncertain pathogenesis. It is often associated with rapidly progressive sensorineural hearing loss (SNHL) but may be unilateral early in the disease (McCabe, 1979, Veldman et al, 1984). The hearing loss may be associated with vestibular symptoms that have a typical fluctuating course during the active phase of disease. Atypically, it may present as fluctuating hearing loss in the only ear (where the opposite ear has profound hearing loss due to a previous event, e.g., Meniere’s).

Although not well studied, circulating autoantibodies against inner ear antigens have been reported, but these are poorly reproducible and not clinically reliable for either diagnosis or treatment of this often devastating disease. AIED is frequently not recognized by clinicians and results in partial hearing loss in virtually all patients, and complete hearing loss in about 1/3 of patients (Alleman et al, 1997, Hughes et al, 1984, Gottschlich 1995, Toubi et al, 1997). Even when AIED is recognized, therapeutic response to corticosteroids, immunosuppressives, and plasmapheresis is incomplete, and highlights the need for better diagnostic and therapeutic modalities for its management (Hughes et al, 1984, McCabe, 1989, Matteson et al, 2000).

The diagnosis and management of immune-mediated hearing loss has been traditionally dependent upon history and limited clinical findings. Laboratory markers of inflammation such as erythrocyte sedimentation rate (ESR), serologic or autoantibody measurements, including the heat shock protein 70 (HSP-70), imaging studies such as magnetic resonance imaging (MRI) or the more invasive arteriogram, and/or histologic examination of biopsied specimens are usually normal and not very helpful, although of these the HSP-70 shows the most promise (Hughes et al, 1984, Harris and Sharp, 1990, Hirose et al, 1999).

Autoimmunity has been proposed as the pathogenesis of sudden SNHL characterizing AIED, although the mechanism of disease is poorly understood. Clinically, sudden SNHL has been seen in association with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and polyarteritis nodosa (Hughes et al, 1984, Summers and Harker, 1982, Andonopoulos et al, 1995) either in the patients themselves or in members of the family. Cogan’s syndrome is accepted as an autoimmune disease, and it is likely that at least some cases of Meniere’s disease, especially when bilateral, are autoimmune in nature (Veldman et al 1984, Hughes et al, 1984, Gottschlich et al, 1995). Circulating autoantibodies against inner ear antigens have been reported as have viral antigens in the endolymph, although the sensitivity, specificity and role of these antibodies in the disease process are poorly defined (Alleman et al, 1997, Kumagami, 1996). The improvement in hearing following corticosteroid and immunosuppressive therapy as well as plasmapheresis further suggests an autoimmune response as the etiology of the hearing loss in these conditions (Veldman et al, 1984). It has been suggested that a nonspecific reactant, heat shock protein 70 (HSP-70), may be predictive of corticosteroid responsiveness (Hirose et al, 1999). It has also been sug-
gested that disturbance of microcirculation in the inner ear by thrombosis associated with antiphospholipid antibodies may lead to sudden deafness, although in our experience these antibodies are infrequently present and of uncertain diagnostic or therapeutic significance (Toubi et al, 1997, Kumagami 1996, Casoli and Tumiati, 1995, Naarendorp and Spiera, 1998).

High doses of corticosteroids, often in doses of 40-80 gm/day, may be useful in the initial management of autoimmune mediated SNHL (Hughes et al 1984, McCabe, 1989). Unfortunately, improvement in hearing is rarely sustained, and unacceptable side effects from the corticosteroid therapy soon follow. To improve the outcome of autoimmune inner ear disease, the use of cytotoxic therapy with cyclophosphamide has been proposed. While some success has been reported with this therapy in slowing or arresting the hearing loss, cyclophosphamide use is associated with significant toxicities, including increased risk of infection, malignancy, and death (Clements 1991). Another chemotherapeutic agent, methotrexate, has been successfully used in low doses for the management of a number of autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, and Wegener's granulomatosis with favorable experience both from a standpoint of efficacy and toxicity (Hughes et al, 1984, Clements, 1991). Based on this experience, methotrexate has also been employed as treatment for autoimmune inner ear diseases, including some cases of Meniere's disease and Cogan's syndrome (Matteson et al, 2000).

At Mayo Clinic, we are actively investigating the pathophysiology, diagnosis and assessment of AIED. There are very few centers in the world where research into this disorder is conducted. Currently, about 80 patients with this disorder are being followed at Mayo in a clinic we have established to evaluate and treat patients with autoimmune hearing loss within the Department of Otorhinolaryngology and the Divisions of Rheumatology and Audiology. This clinic forms the basis of our current research, which includes study of the utility of several therapeutic agents such as methotrexate and etanercept for this disease, utility of assays such as positron emission tomography (PET) and HSP-70 in diagnosing and treating it. To better understand AIED, immunologic and immunogenetic studies are being conducted in Mayo Clinic laboratories by one of the authors (SES) with a colleague in Rheumatology/Immunology to better understand the pathogenesis of this condition.

As part of this effort, we recently completed a one year prospective study of low dose methotrexate to evaluate the long-term efficacy of this therapy in the management of autoimmune hearing loss (Matteson, et al 2001). This study included 17 patients with treatment refractory autoimmune hearing loss. All patients had ongoing episodic worsening of hearing in one or both ears prior to enrollment despite traditional medical therapy. The MTX dose was 7.5 - 25 mg/ week. Hearing loss and vertigo were evaluated at baseline and at completion of the study. Hearing improvement was defined as an improvement in average pure tone threshold (PT) of >10 dB or an increase in speech discrimination (SD) of >15%, while worsening was defined as a decrease of >10 dB in PT or decrease of >15% in SD in at least one ear.

MTX was well tolerated. Among patients with Meniere's, 5 of 9 had improvement or resolution of vertigo. Equilibrium improved in all 3 patients with Cogan's and improved in 2/3 patients with idiopathic hearing loss and this symptom. According to the parameters defined above, hearing improved in 12 patients (71%), was unchanged in 3 patients (18%), and worsened in 2 patients (11%). As a result of this study, we believe that long-term low dose MTX therapy may be a useful therapy for at least some patients who have hearing loss with a presumptively autoimmune-mediated component that is refractory to traditional therapies.

Proper diagnosis and assessment of AIED remains a significant challenge. In an effort to better define disease activity, we have carried out a preliminary study of positron emission tomography (PET) in AIED. To our knowledge, this is the first attempt to utilize PET in the evaluation and characterization of AIED. As suggested by studies evaluating inflammation in other idiopathic inflammatory diseases of the immune system such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus, giant cell arteritis and polymyalgia rheumatica, increased 18-fluoro-2-deoxyglucose (FDG) transport across capillary membranes possibly correlates with glucose uptake in inflammatory foci (Stoppe et al, 1990, Takano et al, 1993, Danfors et al,
We hypothesized that FDG can be utilized in PET to assess disease activity in patients with AIED. The primary outcome measure of the study was whether PET would detect any abnormality (hypo- or hypermetabolism of FDG) on the affected inner ears compared to the controls and whether a difference in FDG uptake would be noted following therapy.

We evaluated ten patients with AIED and five sex and age matched controls without any history of AIED by limited PET of the inner ear. Five patients with new or active AIED underwent serial PET before and after 4-6 weeks of a high dose-tapering course of prednisone. Five patients with an established diagnosis of AIED and stable disease under treatment and 5 controls underwent a single PET scan of the inner ears. Both the study and control subjects had head MRI (for anatomical correlation), audiometric, and vestibular studies, and the AIED patients had heat-shock protein (HSP-70) measurements. Limited PET images of the inner ear using 18-fluoro-2-deoxyglucose (FDG) isotopes were obtained. PET scans were read by two nuclear medicine consultants blinded to the identity and the diagnosis of each subject. The PET was normal in 4/5 normal controls, and abnormal in one with normal audiometric and vestibular studies. Of patients with established and stable AIED, 4/5 had no PET abnormalities and negative HSP-70; and the one with abnormal PET shortly thereafter manifested clinically active disease. Of the 5 patients with active AIED followed serially, 4 had an initial abnormal PET in at least one ear which became normal (definitely negative) in all but one patient after therapy. Only one patient with clinically active AIED had a normal PET before and after therapy (the HSP-70 was positive before therapy and negative after the therapy). We concluded that PET, especially when combined with HSP-70 determination, may be a useful technique for assessing disease activity in patients with AIED.

Currently, we are evaluating etanercept (Enbrel™), a fusion protein consisting of two recombinant p75 tumor necrosis factor (TNF) receptors linked to the Fc portion of human IgG1 as treatment for active AIED (Mohler et al, 1993). The molecule is a powerful antagonist of TNF, binding to and inactivating this cytokine. TNF has been shown to play a critical role in a number of chronic inflammatory conditions (Smith et al, 1990, Beutler et al, 1994, Arend et al, 1996). For the past five years, etanercept has been tested extensively in human trials, including clinical trials in rheumatoid arthritis (RA), juvenile RA, geriatric (age>65) patients with RA, Crohn’s disease, human immunodeficiency virus (HIV) infection, congestive heart failure, allograft rejection and sepsis syndromes (Moreland et al, 1999, Weinblatt et al, 1999, Batson et al, 2000).

The 40 patients enrolled into this 6 month study are assessed by conventional methods including clinical examination, audiometrics, evaluation of vestibular function and HSP-70 testing. In addition, serial PET scanning is being evaluated as a measure of disease activity. This study should provide definitive information about the utility of these approaches to AIED.

**SUMMARY**

AIED is an unusual, but serious condition that may occur in the absence of an associated disease, or as a manifestation of a systemic immune mediated inflammatory disorder. Both diagnosis and treatment are imperfect, and many patients become severely hearing-impaired because of it. While variably effective, agents used in the treatment of AIED have been associated with serious and occasionally life-threatening adverse effects (Clements 1991, Hoffman et al, 1992). Fortunately, many patients may benefit from advances in cochlear implant technologies, and a number of our patients with AIED have undergone this procedure, with generally excellent results. At the same time, our goal is to preserve natural hearing by improved understanding of the pathogenesis, natural history, early diagnosis, and successful treatment of the disease. This latter point is particularly important as not only hearing but balance can be permanently impaired because of the disease, and because AIED may be part of an underlying systemic disorder, the management of which is critical to a satisfactory outcome.

A well integrated, organized multidisciplinary approach is essential to satisfactory evaluation and treatment of AIED. Many patients with this disease have an underlying systemic disorder which requires management of skilled internists, as does the
proper follow-up of long term therapy with immunosuppressive agents because of their many complications. The best outcome for the patient requires the including involvement of knowledgeable otolaryngologists, audiologists, neurologists, internists, and immunologists.

REFERENCES


