Iranian Journal of Otorhinolaryngology
Vol. 22, No.61, Autumn-2010,

Review Article

Autoimmune Inner Ear Disease- A Clinical Viewpoint

Amirala Khalessi[1], Pedram Borghei[2], *Mohammad Hassan Khalessi[3]

Abstract

Recent developments in medicine have given us a better insight into a group of disorders known as autoimmune diseases. In particular, advances have occurred in our understanding of the Autoimmune Inner Ear Disease (AIED). In this article, the authors review the different postulated theories in the pathogenesis of this disease. The clinical presentation, the available para-clinical diagnostic tools, and the important differential diagnoses will be summarized. The management methods, including steroid therapy, immunosuppressive medications, other biological agents and intra-tympanic injections, will be addressed. Cochlear implantation as a final solution to the advanced stages of the disease, causing total deafness, will also be discussed.

Keywords:
Autoimmune, Disease, Inner ear

Received date: 1 May 2010
Accepted date: 17 Aug 2010

[1] *Royal Prince Alfred Hospital, The University of Sydney, Sydney, Australia*
[2]*Department of otorhinolaryngology, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[3]*Department of otorhinolaryngology, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran*
Corresponding author:
Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran
Email:drkhalessi@ymail.com, Tel:+982166703037

Introduction:

Autoimmune Inner Ear Disease (AIED) is a phenomenon resulting from the deleterious effects of autoantibodies or immune cells on the inner ear. While in primary AIED, immune reactions and their subsequent damages all occur in the inner ear, other immune conditions may affect the inner ear secondarily as a result of immune-mediated reactions that occur systemically or primarily in other organs. The latter is referred to as immune-mediated inner ear disease. Some systemic autoimmune diseases may involve the cochleo-vestibular system. This group of conditions are referred to as secondary AIED by some authors (1-16).

Despite the described differences in pathogenesis, the clinical features of AIED comprise a syndrome of, and asymmetrical sensorineural hearing loss with or without dizziness or buzzing, which takes weeks or months to develope, and may show some fluctuations. AIED is more prevalent in ages between 20 to 40, however, there are cases of immune-mediated cochleo-vestibular disorders in children (14), particularly when accompanied by systemic autoimmune diseases.

Autoimmune Theories:

Although the exact details of autoimmune reactions have not been fully identified, the results of antigenic stimulation, antibody formation and/or T-cell activation when encountering autoantigens, depend on the same factors that exist when there is an external antigens.

To explain an abnormal autoimmune response, a number of theories have been proposed (1):

There may be a reaction to an antigen which does not normally occur in blood circulation. This antigen, known as the hidden antigen, can be from milk casein, eye lens proteins or certain protein molecules found in the reproductive system. The problem in identifying an antigen as a hidden antigen is that the available laboratory tests may lack the adequate sensitivity to trace the antigen when in small quantities. Hidden antigens may not be recognized as self-antigens, and can create an immune response upon entering the blood circulation. This happens in sympathetic ophthalmia through the traumatic release of the eye's hidden antigen. A similar condition can occur in the ear, which is known as sympathetic cochleopathia. Other clinical examples include sudden or progressive sensorineural deafness that appears in the opposite ear years after the patient experiences hearing loss caused by trauma or infection.

Another theory involves the potential for immunogenicity of chemical, physical and biological agents. Mutations can result in what is normally a self-antigen to provoke an immune response. Mutations may occur either spontaneously or as a result of external factors such as viral infection. A chemical bond formation between a self-antigen and a Hapten may result in an immune response against the newly formed antigen. Physical factors such as the ultraviolet light, infrared rays, and thermal energy influence body proteins, which may result in changing the nature of self-antigens.

A third mechanism is a response to a self-antigen after exposure to a non-self-antigen. In this theory the self antigen has a structure that mimics that of the external antigen, thus, any reaction to the common structure can be against both the external and the self-antigens. To date, there has been no report of sensorineural deafness based on mechanisms 2 and 3.

The autoimmune phenomenon may be an epiphenomenon, and the early pathogenesis may result from an immune response to an antigen such as one from a virus. For instance, the antigenic characteristics of some cells or cellular elements may be changed by viral infection of the inner

ear, resulting in a local immune reaction in the inner ear.

Finally, several genetic mutations occurring during the immunological development, may impair the tolerance phenomenon, due to the loss of immune adjustability.

There is evidence to suggest that the genetic defects in the immune system may predispose to AIED. Studies show an association between different HLA types and AIED.

Prevalence and Clinical Features:

AIED is not a common disease, comprising less than one percent of cases of sensorineural deafness. However, the fact that the disease appears and progresses in critical stages of life (20 to 40 years of age) and is often resistant to treatment, renders it of high importance (13,14).

Sensorineural hearing loss is accompanied by dizziness in 50% of patients with AIED. Approximately 16% of cases of bilateral Meniere's disease and 6% of all cases of Meniere's disease have an autoimmune origin (8-14).

The isolated involvement of the vestibular system is quite common in AIED, but due to lack of specific diagnostic tests, AIED prevalence cannot be determined precisely Only one percent of all balance disorder are said to have an autoimmune origin.

The clinical symptoms of AIED include general imbalance, ataxia, intolerance to movement, fits of acute vertigo, and positional vertigo. The oscillopsia which results from bilateral weakness of the vestibular system has been reported in 5% of patients with autoimmune disease (16).

Balance disorders with a central origin may appear in immune-mediated diseases including multiple sclerosis, brainstem encephalitis and vasculitis.

AIED Diagnosis:

The diagnosis of AIED is possible through patient's history, clinical findings, laboratory tests, vestibular and audiometry tests, and in particular the response to immunosuppressive therapies (4).

Immunologic Laboratory Tests:

Although specific autoimmune tests are always popular, there is no sufficiently effective and readily available tests to meet the needs in this field. Further, there is no clear relationship between the discovered antigens and the pathology of the inner ear.

Various antigenic proteins have been identified and analyzed in recent years. Heat Shock Protein 70 (HSP 70), an auto-antigen with a molecular weight of 68KD, is probably the most recognized auto-antigenic protein. There is no proven relationship between anti-HSP 70 antibodies and AIED. Researchers believe that anti-HSP 70, also known as anti-cochlear antibody, is not sufficiently specific.

The low specificity and sensitivity of these tests, as well as the inaccessibility of test-centers, have limited their routine usage.

The current diagnostic tests that are in use are non-specific, some of which in order of usefulness are as follows:

ESR and CRP
ANA
Thyroid antibodies (antimicrosomal and thyroglobulin)
Rheumatoid factor
Complement C1q
Smooth muscle antibody
Lupus anticoagulant
Anticardiolipin antibodies
HLA testing (HLA- B27)
FTA
HbA1c
HIV
Lyme titer

Differential Diagnosis of AIED:

The diagnosis of AIED is based on the precise evaluation of the patient's history, clinical findings and response to immune suppressive therapies. Laboratory tests and imaging may be helpful in confirming the diagnosis or ruling out other diseases.

MRI may show the enhancement of the cochlea in patients with the autoimmune disease. There are several studies showing the effectiveness of PET Scan in the diagnosis of the disease, yet more studies are required in this field. The differentials that must be considered are:

Auditory neuropathy may appear as bilateral progressive sensorineural hearing loss. Audiometry tests including OAE and ABR may be useful in diagnosing the disease.

Late-onset genetic deafness may appear in bilateral and progressive forms. However, in comparison with progressive autoimmune deafness, the progression of late-onset genetic deafness is very slow.

Cochlear otosclerosis may appear in bilateral and progressive forms, especially because autoimmunity is one of the proposed mechanisms in etiopatogenesis of the disease. However the difference lies in the slower progression and the lower prevalence (2-9).

Congenital deafness in neonates may occur because of an autoimmune origin. Studies have shown that idiopathic congenital and sensorineural deafness is far more prevalent in neonates whose mothers suffer from an autoimmune disease (10).

Sudden idiopathic deafness may be considered in the differential diagnosis. Sudden idiopathic deafness which may sometimes have an autoimmune origin is far more common than AIED, and is unilateral. Sudden idiopathic deafness is an otological emergency, with a therapeutic time window of 2 to 4 weeks. On the other hand, bilateral progressive immunogenic deafness does not require urgent treatment, and high doses of corticosteroids or immunosuppressive drugs can bring about considerable improvement even 6 months to one year after onset of the disease.

Otolaryngologists are generally aware that some types of sensorineural hearing loss can be treated with corticosteroids. However, little attention may be paid to the fact that sudden sensorineural deafness and the progressive type in AIED are completely different in their response to steroid therapy, and that short-term steroid treatments may lead to delayed diagnosis of bilateral progressive immunogenic deafness and may also interfere with serological tests (1).

Current Treatment Approaches for AIED:

Although the etiopathogenesis of AIED is not well understood, its clinical manifestation is well-recognized, and in many cases is responsive to immunosuppressive therapies (11).

Corticosteroid tops the list of the immunosuppressive therapies.

There are some controversies as to the mechanism of action of corticosteroids in the treatment of AIED. While the anti-inflammatory effects of immunosuppressive glucosteroids are well-recognized, since they can also affect mineralocorticosteroids receptors, their therapeutic effects may be due to water and electrolytes regulation in the inner ear. To test this possibility, researchers have tested aldosterone and prednisolone on mice and have observed similar results. According to follow-up studies, aldosterone does not have any role in decreasing the quantity of antibody complexes that happens with the use of prednisolone. Thus, it seems logical to believe that the therapeutic effects of prednisolone are partly due to its immunosuppressive effects on decreasing antibody complexes and partly due to its mineralocorticosteroid effects on electrolytes balance.

These findings play an important role in the development of AIED therapeutic procedures in future.

Use of high dose steroid is now a standard therapeutic procedure for AIED. The first

phase of treatment includes prednisone or prednisolone 60 mg daily for 4 weeks. If a positive response is observed a second phase is started. This phase includes lower doses of prednisone or prednisolone and can continue for 18 weeks with the average daily dose of the medication being 30 mg. Naturally, minor changes to this protocol are possible; however, experiments have shown that treatments of less than 6 months duration have a higher risk of relapse. Although there are side effects associated with high dose steroid therapy, proper patient selection, continuous monitoring and patient training can render this therapy effective and safe. Other immunosuppressive medications used include methotrexate, cyclophosphamide, azathioprine and cyclosporine-A. These second-line medications are usually administered in addition to steroids. If no response to steroids, they can be omitted from the therapeutic protocol. (15).

Methotrexate, which was once considered a promising treatment, has recently yielded disappointing results in some patients. As for cyclophosphamide, azathioprine and cyclosporine-A, there have been insufficient experiments and controversies regarding their effectiveness. The side effects of Cyclophosphamide outweigh its potential benefits.

Biological Agents:

Discovering biological agents which target inflammation-generating cytokines (such as IL-1 and TNF) has revolutionized the pathophysiological understanding of inflammatory diseases. Among these agents, etanercept and infliximab (antagonists of TNF) have been highly considered.

Etanercept 25 mg (Enbrel®) has been administered as a biweekly subcutaneous injection. However, due to the controversies surrounding its therapeutic effects as well as its high costs, it is not routinely used.

Intratympanic Therapy:

Injection of steroids and other immunosuppressive medications into the middle ear to prevent their systemic side effects has become more common in recent years and in some cases has reduced the required dose of steroids. Etanercept, infliximab and even methotrexate have been used intratympanically with variable success.

Immune modulating drugs employed in intratympanic therapy such as alpha and beta interferon and others that reduce immune response (such as minocycline) are yet to be adequately studied in treatment of AIED.

Other therapeutic procedures include gamma globulin injection (IVIG) and plasmapheresis (when routine treatments have failed).

Cochlear Implant in AIED:

Despite the existence of anti-inflammatory, immunosuppressive and other therapeutic procedures, some patients with AIED and systemic autoimmune disease with sensorineural deafness gradually, and at times suddenly, develop total deafness. This trend is more common in Cogan disease and in autoimmune disease accompanied by vasculitis.

Since most of these patients are post-ligual-adults with short-term deafness, they are suitable candidates for cochlear implant (CI).

On the other hand, vascular degenerative changes in the blood supply of the inner ear that occur in AIED and result in decreasing cochlear blood circulation, may lead to cochlear fibrosis and ossification, resulting in the occlusion of the inner cochlear space.

Therefore, to evaluate patients with autoimmune disease who are candidates for cochlear implant, high resolution CT, MRI (with Gadolinium) should be considered (1,2).

Final Word:

Clinical findings remain most highly considered in the diagnosis of AIED, and high dose corticosteroids, and in some cases immunosuppressive drugs comprise the mainstay of treatment. The absence of a thorough understanding of etiopathogenesis of AIED, the low incidence of the condition, which limits research on large groups, and the absence of a proper animal model have slowed development in this field.

Further research is necessary to understand various aspects (and forms) of the disease and to develop diagnostic tests and targeted therapies.

References:

1. Khalessi MH. [Autoimmunity and Ear Disease (Otoimmunity)]. Tehran: Tehran University of Medical Sciences; 2003. (Persian)
2. Agrup C. Immune-mediated audiovestibular disorders in the pediatric population: A review. Int J Audiol 2008; 47(9): 560-5.
3. Aftab S, Semaan Mt, Murray GS, Megerian CA. Cochlear implantation outcomes in patients with autoimmune and immune-mediated inner ear disease. Otol Neurotol 2010; 31(8): 1337-42.
4. Alexander TH, Weisman MH, Derebery JM, Espeland MA, Gantz BJ, Gulva AJ, et al. Safety of high-dose corticosteroids for the treatment of autoimmune inner ear disease. Otol Neurotol 2009; 30(4): 443-8.
5. Bovo R, Ciorba A, Martini A. Vertigo and autoimmunity. Eur Arch Otorhinolaryngol 2010; 267(1): 13-9.
6. Bovo R, Ciorba A, Martini A. The diagnosis of autoimmune inner ear disease: Evidence and critical pitfalls. Eur Arch Otorhinolaryngol 2009; 266(1): 37-40.
7. Bunile MC, Geelan -Hansen K, Weber PC, Tuohv VK. Immunosuppressive therapy for autoimmune inner ear disease. Immunotherapy 2009; 1(3): 425-34.
8. Chau JK, Lin JR, Atashband S, Irvine RA, Westerberg BD. Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. Laryngoscope 2010; 120(5): 1011-21.
9. Dayal VS, Ellman M, Sweiss N. Autoimmune inner ear disease: clinical and laboratory findings and treatment outcome. J Otolaryngol Head Neck Surg 2008; 37(4): 591-6.
10. Hervier B, Bordure P, Audrain M, Calais C, Masseau A, Hamidou M. Systematic screening for nonspecific autoantibodies in idiopathic sensorineural. Otol Neurotol 2010; 31(4): 687-90.
11. Karosi T, Szekanecz, Sziklai I. Otosclerosis: An autoimmune disease? Autoimmun Rev 2009; 9(2): 95-101.
12. Buniel MC, Geelan-Hansen K, Weber PC, Tuohy WK. Immunosuppressive therapy for autoimmune inner ear disease. Immunotherapy 2009; 1(3): 425-34.
13. Rawal SG, Thakkar KH, Ziai K, Santi PA, Djalilian HR. HLA-B27-associated bilateral Meniere disease. Ear Nose Throat J 2010; 89(3): 122-7.
14. Schrauwen I, Van Camp G. The etiology of otosclerosis: A combination of genes and environment. Laryngoscopye 2010; 120(6): 1195-202.
15. Tan CQ, Dong WD, Guo L, Huang H, Wang DY. Auditory function in women with autoimmune inner ear diseases and their offspring. Int J Pediatr Otorhinolaryngol 2009; 73(12): 1702-11.
16. Yukawa K, Hagiwara A, Ogawa Y, Nishiyama N, Shimizu S, Kawaguchi S, et al. Bilateral progressive hearing loss and vestibular dysfunction with inner ear antibodies. Auris Nasus Larynx; 37(2): 223-8.