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REVIEW ARTICLE

Demystifying autoimmune inner ear disease

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Abstract

Introduction Autoimmune inner disease (AIED) is an uncommon cause of sensorineural hearing loss and poses a diagnostic challenge. The present study aims to review the existing knowledge on the clinicopathological aspects, the diagnostic challenges, and therapeutic interventions in AIED.

Discussion The incidence of AIED is less than five cases per 100,000 population. There are no definite seromarkers which make diagnosis of AIED difficult. Even though various markers have been studied, their sensitivity and specificity have not been replicated in the clinical scenario. The treatment of the condition is also an enigma. Corticosteroids are the drug of choice and require long-term use to prevent relapse. Various other therapeutic agents have been studied in a small cohort of patients, but the efficacy of these drugs needs to be validated in a large multicentric trial.

Conclusion Timely intervention can restore hearing loss in AIED patients, but the clinician has to find a delicate balance between the hearing outcome and the potential side effects resulting from long-term use of the drugs. Treatment of steroid resistant AIED is a challenge and there are no universal guidelines for the same. AIED being an uncommon diagnosis, multicentric trials and collaboration are required to formulate diagnostic criteria and therapeutic guidelines.

Keywords Inner ear · Autoimmunity · Hearing loss · Sensorineural · Diagnosis · Inner ear antigens · Circulating antibodies · Positron emission tomography · Magnetic resonance imaging

Introduction

Autoimmune inner ear disease (AIED) was first described by Cogan in 1940 [1] and then by Lehnhardt in 1958 [2]. The diagnosis of AIED is challenging as there are no definite serological and radiological criteria. The time course of evolution of symptoms is an important diagnostic clue as the progression of hearing loss in autoimmune hearing loss occurs "over weeks or months and not hours nor days nor years" [3]. It may be primary when the pathophysiology is limited to the ear itself. Secondary cases occur due to underlying systemic autoimmune disorders [3]. AIED is a distinct clinical entity from sudden sensorineural hearing loss (SSNHL) and its incidence is less common than SSNHL. The incidence of SSHNL is estimated at 5–30 cases per 100,000 per year [4–6]. The incidence of AIED has been estimated to be less than 5 cases per 100,000 per year with an estimated prevalence of 45000 [1] in the US. The prevalence rates of the condition can be misleading as AIED has remained an enigma for the otologist due to its lack of universal diagnostic markers.

Pathophysiology of autoimmune inner ear disease

The inner ear has been considered as an immune-privileged site due to the presence of the blood labyrinthine barrier [7]. The presence of tight junctions at blood labyrinthine barrier was considered to block the immune cells and antibodies. However, recent studies refute such opinion and a large number of macrophages and immune-competent cells have been found in the endolymphatic sac in the inner ear [8]. The normal cochlea is devoid of lymphocytes. However, in response to inflammation immune-competent lymphocytes reach the

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cochlea from the systemic circulation through the spiral modiolar vein. The recruitment of immunocompetent cells occurs in response to various inflammatory mediators like IL 2, IL 1β and TNF α [9]. Apart from the cytotoxic T cell-mediated injury, the inner ear is also affected in a multitude of systemic inflammatory diseases. The mechanism of such injury is usually Type III reactions mediated by the deposition of immune complexes into the endothelial surfaces of the inner ear vasculature resulting in sensorineural hearing loss. Type IV immune reactions have been established in animal models and it is strongly believed that a similar mechanism of pathogenesis may also cause sensorineural hearing loss in patients [9]. The mechanism of autoimmunity of the inner ear can be explained by two theories. The "cross reactions" theory is the most accepted theory and states that 'antibodies or rogue T cells' cause accidental damage to the inner ear as it shares common antigens with the virus, bacteria which the immune system fights. The other mechanism called 'sympathetic cochleolabyrinthisis' states that the lymphocytes become sensitized to various inner ear proteins as a result of exposure of the proteins in the damaged cochlea. Such damage may be caused by infections, ischemia and iatrogenic trauma to either of the ears [10].

Western blot analysis in patients of SSNHL revealed antibodies against specific inner ear antigens like cochlin, β-tectorin and HSP-70. These antigens are distributed across various regions in the inner ear like the spiral limbus, spiral ligament, basal hair cells, supporting cells, cochlear as well as vestibular labyrinth [9, 11]. Besides these, there are other proteins like KHRI-3 which is expressed in the wall of the saccule, utricle and the endolymphatic sac and supporting cells. Type II collagen is expressed in the subepithelial layer of the endolymphatic duct and the spiral ligament [9]. All these proteins can be the potential target in immune mediated hearing loss.

Clinical features

AIED is an uncommon disease and true incidence rates are difficult to determine. Lack of specific diagnostic and laboratory criteria contribute to under diagnosis of the condition. AIED is more common among females than in males. The initial age of presentation is usually between 20 and 50 years [12]. AIED can present with progressive sensorineural hearing loss or as sudden sensorineural hearing loss (SSHNL) which is progressive. The common presenting symptom is that of a rapidly progressive, often fluctuating, bilateral sensorineural hearing loss. The symptoms may be unilateral at the onset but eventually almost 80% of the patients have involvement of both the ears. The progression of the hearing loss usually occurs over weeks to months. SSNHL may show a flat audiogram indicating involvement of all frequencies or may involve the lower frequencies. High-frequency involvement with accompanying vertigo has worse outcome [13–15]. A clinical criteria has been proposed by Berochal for clinicopathological diagnosis of AIED. Three positive major criteria or two positive major and two minor criteria can raise the suspicion of AIED in the absence of a specific seromarker or a diagnostic test [16] (Table 1).

Cogan syndrome is a distinct form of AIED with involvement of the eyes and inner ear and manifests as interstitial keratitis with audiovestibular symptoms [17]. Vestibular symptoms are seen in almost 50% of the patients and include episodic or positional vertigo, disequilibrium, ataxia and or motion intolerance. Tinnitus is an accompanying symptom in almost 25–50% of patients and can be confused with Meniere's disease [10, 18–20]. Isolated involvement of the vestibular system is common but due to lack of diagnostic criteria, many balance disorders of autoimmune origin are missed. It is estimated that about 1% of balance disorders may be of autoimmune origin [21].

Diagnosis

Clinical examination of the ears is usually normal and standard audiological test battery is used for the confirmation of the sensorineural hearing loss. The suspicion of AIED can be made on pure tone audiogram based on Rauch criteria which is "bilateral sensorineural hearing loss of at least 30 dB at any frequency and evidence of progression in at least one ear on two serial audiograms performed 3 months apart. Progression of hearing loss in AIED manifests as a "threshold shift of 15 dB at one frequency, 10 dB at two or more consecutive frequencies, or a significant change in discrimination score" [22]. The involvement of the stria vascularis, spiral ligament and the Organ of Corti in AIED causes cochlear hearing loss. A retrocochlear hearing loss

Table 1 Clinical criteria for AIED [16]

Major criteria	Minor criteria
Bilateral involvement	Unilateral involvement
Presence of systemic autoimmune disease	Young middle aged female
High levels of Antinuclear antibody	Serum reactivity against HSP70
Reduced number of naïve T cells (CD4RA)	Positive response to steroid treatment (recovery rate < 80%)
Recovery rate of more than 80%	

may occur due to ischemia secondary to immune complex deposition. Few cases of secondary AIED may cause conductive hearing loss due to rheumatoid arthritis affecting the incudostapedial joint or middle ear effusion resulting from polyangitis [23]. A prospective study demonstrated the efficacy of the use of mobile tablet audiometry in the home setting to identify the fluctuations in hearing level and the response to treatment. Though not commonly used, mobile audiometry can be a practical approach to monitor the hearing levels in patients with AIED and their response to treatment [24]. The presence of inflammatory joint disease, ocular inflammation in the form of non syphilitic keratitis, inflammatory swelling of the thyroid and or any immune mediated disorder suggest associated systemic inflammatory immune disease. A detailed workup involving the hematological, biochemical and radiological evaluation is often necessary to identify or rule out underlying systemic immune disorder [25] (Table 2).

Serological markers for AIED

There are no diagnostic markers for AIED at present. Immune biomarkers associated with systemic inflammatory and autoimmune disorders lack specificity and have been used to rule out associated systemic immune disorders.

HSP 70 previously called 68 kDa protein has been evaluated as a possible diagnostic serological marker. It has a good specificity but is limited by low sensitivity [26, 27]. A systematic review and meta analysis show a pooled sensitivity of 75% and a specificity of 98% of HSP 70 antibodies. However, the study was limited by a small sample size [28]. The presence of serum antibody to 68 kDa was found to have a favorable outcome to corticosteroid treatment [29].

A separate protein 30 kDa was evaluated as a possible marker of the AIED and was demonstrated to be a major peripheral myelin protein (P0). P0 is a glycoprotein belonging to a family of cell adhesion molecules and is present in the Organ of Corti, spiral ganglion and the auditory nerve. P0 plays an important role in the autoimmunity in the inner ear [30]. However, multicentric study has failed to demonstrate any significant alteration in the serum levels of P0 in the AIED group [31].

Serum anti-endothelial cell antibodies (AECA) have also been detected in patients with autoimmune inner ear disease. The presence of these antibodies in the sera of patients with AIED have been found to have worse outcome in terms of hearing recovery and responsiveness to steroids [32]. As such AECA may be used as a marker for prognosis of the hearing loss. Further validation of its role as a prognostic marker is required before incorporating the test in routine workup of AIED.

A cytoskeleton protein β-actin found in the supporting cells as well as stria vascularis and β-tubulin found in the epithelium of the endolymphatic sac has been evaluated as a possible target antigen in AIED. Antibodies against the protein has been detected in the sera of patients of AIED. However, its application as a diagnostic or prognostic marker is awaited [33, 34].

The search for potential diagnostic biomarkers for AIED continues and the present focus is on circulating microRNA (miRNA). Studies in mouse AIED models have identified their potential for early diagnosis of AIED. However, its application in clinical cases of AIED is awaited [35].

Magnetic Resonance Imaging (MRI) with gadolinium contrast must be undertaken to rule out lesions in the internal auditory canal and the posterior fossa. There are no radiological criteria for the diagnosis of AIED and the radiological signs on MRI are nonspecific. MRI with contrast

Table 2 Diagnostic approach for suspected case of AIED

Clinical	Laboratory/serological	Radiological
Bilateral SNHL progressing over weeks to months Normal otoscopic examination Evidence of systemic immune disorder may or may not be present	Complete blood count ESR Antinuclear antibodies Rheumatoid factor Anti double stranded DNA Anti SSA/B antibodies Antiphospholipid antibodies Anti TPO antibodies VDRL Lyme's test HIV FTA–ABS C3, C4 levels HLA typing Anti HSP 70 Lymphocyte migration test	MRI with contrast (to rule out retrocochlear causes of hearing loss)

has failed to show any evidence of post-contrast changes in the inner ear in AIED patients [36]. A study by Lobo et al. conducted in 17 patients with clinical suspicion of AIED revealed evidence of endolymphatic hydrops on MRI with intratympanic gadolinium contrast administration. Even though the study had a small sample size and lacked control arm, it provided evidence of the morphological changes in the inner ear secondary to AIED. MRI with intratympanic gadolinium contrast study is yet to be established in a large sample [37]. Presently there is no role of PET scan in the diagnosis of AIED even though a pilot study has shown an abnormal uptake in the inner ear in patients with active AIED [38].

The association of HLA has been studied in AIED and it is seen that HLA–DR4 is absent in almost 80% of the patients. The presence of HLA-B35, CW4 and CW7 on the other hand indicates a propensity to develop AIED [39, 40]. The phenotypic characterization of lymphocytes reveals a reduction in CD4+ and CD8+ lymphocytes [15]. The Lymphocyte transformation test with Type II collagen has shown a high stimulation index and is considered as a reliable test to detect immune mediated hearing loss [41]. The test has a specificity of 93% and a sensitivity of 50–80% [42]. However, it is not widely available at present as the results are controversial [10].

Despite the presence of various potential immunomarkers, AIED remains a diagnosis of exclusion. A presumptive diagnosis of AIED can be made based on a triad of clinical presentation with audiological findings, exclusion of other known causes of hearing loss and a positive response to immunosuppressive therapy [23]. The presence of seromarkers in the blood of the suspected patients can act only as corroborative evidence of immune mediated hearing loss and their absence does not rule out AIED. A confirmatory diagnostic test or criteria is presently not available and search for the same could be an area for further research. Awareness of the entity is important so that a rational diagnostic approach is undertaken to improve the case detection.

Treatment

The treatment of AIED should be started at the earliest. Early treatment prevents irreversible hearing loss. Treatment should be offered on suspicion of AIED with other possible causes ruled out. The patient must be a part of an informed decision making process and all the pros and cons of treatment clearly explained.

Evidence suggests that steroids improve the hearing in AIED. Oral Prednisolone is usually started at a dose of 60 mg (1 mg/kg/day) and should be continued for a minimum of 4 weeks [43]. In the presence of improvement in hearing, it should be continued and gradually tapered over 6 months. If no response is noted after 4 weeks, tapering is done over 12 days [3]. Inadequate dosing and duration of treatment should be avoided as it causes relapse and poor control [43]. The mechanism of action of corticosteroids is due to its anti-inflammatory properties. Corticosteroids help in the reparative process of the pathological breakdown at the blood labyrinthine barrier. It also helps restore the strial function [44, 45]. Disease flare ups during treatment may require increasing the steroid dose or adding an immunosuppressant to prevent irreversible hearing loss [46]. The long term use of corticosteroid is a concern due to the potential adverse effects and the otolaryngologist has to strike a delicate balance to achieve the minimum required dose for prevention of disease progression. Intratympanic steroid injection has also been evaluated for autoimmune hearing loss. The mechanism of action of the intratympanic steroid occurs through the round window membrane resulting in high concentration in the inner ear without systemic toxicity [47, 48]. Intratympanic methylpednisolone was found to have the highest concentration in the perilymph when compared with dexamethasone and hydrocortisone and is effective in patients refractory to intratympanic dexamethasone [49, 50]. Intratympanic methylprednisolone is usually used at a dose of 0.3–0.5 ml of 40 mg/ml solution at weekly intervals for a period of 8 weeks [51].

Various other cytotoxic and or immunosuppressant drugs like Methotrexate, Cyclophosphamide have been tested as an alternative or as an adjunct to steroids. The results have been ambiguous and a multicentre randomized control trial is required to establish their therapeutic efficacy as an alternative to steroid [52–54]. Currently, these drugs are used in combination with steroids to reduce the adverse effect of high dose steroids. These are also used in steroid non-responders as an alternative therapy (Fig. 1).

Newer therapeutic agents have been studied in small cohorts of AIED patients where steroid tapering was unsuccessful. These include TNF-alpha inhibitors/monoclonal antibodies like Golimumab, Infliximab and Etanercept [55]. Local instillation of Infliximab drops weekly for 4 weeks has allowed successful steroid tapering, shown hearing improvement and maintained a stable hearing 10–38 weeks after treatment [56]. Systemic administration of Etanercept at a dose of 25 mg twice weekly has not shown any significant improvement in the hearing level [57]. The role of IL 1β in the pathogenesis of AIED has led to the study of IL 1β blockers like Anakinra in AIED. Anakinra can be effective in reversing the steroid non-responsiveness. A clinical trial conducted among 14 steroid nonresponders found Anakinra to be effective in improving the hearing threshold. Anakinra can be a potential therapeutic agent and the efficacy of the same needs to be confirmed by further study [58]. Rituximab, a CD20 antagonist has been shown to reduce the steroid dosage

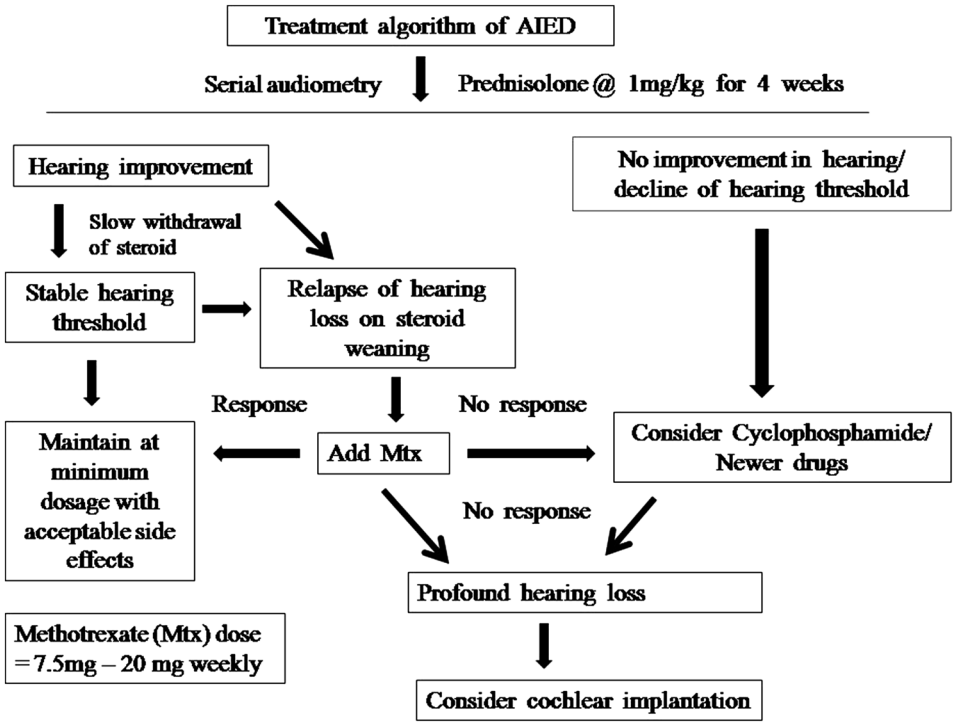

Fig. 1 Treatment of AIED

and improve the symptoms in AIED patients [2]. A study in a small group of 7 patients has shown some promise in maintaining hearing improvement after steroid use [59]. However, at present there is not enough evidence to recommend these biological agents as an alternative to steroid therapy in AIED.

Azathioprine a purine analog was also assessed for its efficacy in the treatment of AIED. A study conducted among 12 patients with AIED and receiving 30 mg prednisolone along with 1 mg/kg Azathioprine found a statistically improved hearing threshold in the patients. However, the study had a limitation as there was no control arm and the patients concomitantly received corticosteroid which could have resulted in improvement of hearing threshold. As such there are no recommendations on the use of Azathioprine [60].

The various cytotoxic and biological agents studied so far have shown promise in the treatment of AIED. However, it is recommended that these drugs should not be used as a first line therapy. Corticosteroids have been time tested modality and should be started as the first line therapy and continued for a minimum of 4 weeks before tapering is started. Almost 50–70% of cases are steroid responsive [3]. Adjunctive therapy with immunosuppressive agents may be recommended in cases where high dose steroids are contraindicated or in cases of relapse of hearing loss during the maintenance or steroid weaning phase. Treatment of steroid resistant AIED is challenging and currently there are no universal guidelines for the same.

Plasmapheresis

The role of plasmapheresis in AIED is to remove circulating antibodies, antigen, immune complexes and other immune mediators from the blood. In this technique, blood is taken from the patient and centrifuged to remove the antibodies, antigens and or immune complexes and then re-suspended in a fresh plasma or albumin in saline before returning to the circulation [10]. Leutje in his series of eight patients found audiometric improvement in patients undergoing plasmapheresis [61]. Plasmapheresis is usually carried out thrice weekly for the first 2 weeks followed by weekly for another 4 weeks. It is effective in removing the effect of circulating antibodies and immune complexes by 65% [10]. Plasmapheresis is useful in severe cases of autoimmune diseases with vasculitis or organ involvement despite adequate immunosuppressive therapy [62]. Plasmapheresis may be helpful in steroid resistant cases as an adjunctive treatment in primary AIED patients with high antibody titres or secondary AIED with coexistent systemic autoimmune disease.

Cochlear implant

Cochlear implant helps in restoring the hearing loss in patients with sensorineural deafness resulting from AIED. It has no role in modifying the autoimmune mediated disease process in the inner ear. Bilateral profound sensorineural hearing loss due to primary or secondary AIED are good candidates for cochlear implantation. Cochlear implantation in such patients

can be technically challenging due to the presence of fibrosis and ossification which may cause difficulty in electrode insertion during the surgery [63]. A thorough preoperative evaluation and planning are necessary to overcome such a scenario. Early implantation is recommended in patients with associated Cogan syndrome and bilateral profound sensorineural hearing loss due to chances of endosteal reaction and neo-ossification of the intracochlear ducts [17].

Newer dimensions in the treatment of AIED

AIED has been a conundrum for the otologists and a challenge due to the absence of specific criteria for diagnosis and prognosis. The complex anatomical structure of the inner ear precludes histopathological evaluation of the diseased ear and drug delivery to the site of pathology.

Intratympanic drug administration with absorption through the round window membrane has been traditionally used as a route for entry into the inner ear. However, it has been seen that the concentration of the drug in the cochlear fluid achieved through this route is suboptimal. Novel drug delivery systems are required to optimize the concentration of the drugs in the inner ear to have a maximum therapeutic effect. Nucleic acid therapy and drug delivery with gene modified macrophages are newer dimensions under research [64]. Nanoparticle delivery systems provide an exciting area of research and are currently under study. It may be possible in near future to conjugate drugs on to nanoparticles and target specific sites in the inner ear [65]. The advantage of such an approach is higher drug concentration at the specific target site and minimal systemic side effects.

Gene therapy directed towards neuronal preservation, hair cell generation and activation of anti-inflammatory pathways are being explored which offers the possibility of restoring hearing loss in AIED [66]. Stem cell therapy is a promising avenue of research for the restoration of hair cells. Human adipose derived mesenchymal stem cells have immunomodulatory properties and have shown hearing improvement in autoimmune sensorineural hearing loss animal models [17]. Clinical trials with stem cells in AIED are limited but occasional clinical reports do show improvement in hearing status with stem cells [67]. There are various challenges relating to the successful homing in of the stem cells to the site of interest, its in vivo survival in the human inner ear and the cost effectiveness of treatment. If successful, stem cell therapy can revolutionize the hearing loss arising from AIED and various other causes [68].

Conclusion

AIED is an important cause of hearing loss and must be kept in the differential diagnosis of progressive sensorineural hearing loss. Unilateral sensorineural hearing loss must be followed up to detect the progression of hearing loss and involvement of the other ear. In the absence of specific serological markers, a high index of suspicion is required to diagnose the condition early. Corticosteroids remain the drug of choice in AIED. Timely intervention can restore hearing loss in such patients but the clinician has to find a delicate balance between the hearing outcome and the potential side effects resulting from long term use of the drugs. It is imperative to follow up the patients with serial audiometry during the treatment phase to assess the hearing outcome. Treatment of steroid resistant AIED is a challenge and there are no universal guidelines for the same. AIED being an uncommon diagnosis, multicentric trials and collaboration are required to formulate diagnostic criteria and therapeutic guidelines.

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Compliance with ethical standards

Conflict of interest The author declares that they have no competing interests.

Research involving Human Participants and/or Animals No human participant and/or animals were used in the study.

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