Review

Autoimmune sensorineural hearing loss: the otology–rheumatology interface

Tamara Mijovic¹, Anthony Zeitouni¹ and Inés Colmegna²

Abstract

Autoimmune sensorineural hearing loss (SNHL) is a rare clinical entity characterized by a progressive fluctuating bilateral asymmetric SNHL that develops over several weeks to months. Vestibular symptoms, tinnitus and aural fullness are present in up to 50% of patients. Due to the lack of specific diagnostic tests, both clinical suspicion and responsiveness to corticosteroids are the pillars for the diagnosis of autoimmune SNHL. The evaluation of patients in whom this condition is suspected should include a detailed history and physical examination, an audiogram, an MRI and a limited laboratory workup to exclude secondary causes of hearing loss. The low frequency of this condition, the heterogeneity in the designs of the available studies and the absence of randomized trials comparing treatment responses and assessing long-term outcomes are some of the factors accounting for the limited evidence to guide the clinician in the approach to the diagnosis and treatment of autoimmune SNHL.

Key words: hearing, deafness, autoimmune inner ear disease (AIED), sensorineural hearing loss (SNHL), autoimmune cochleopathy, immune-mediated cochleovestibular disease, fluctuating hearing loss.

Introduction

Sensorineural hearing loss (SNHL) results from dysfunction of the inner ear, the vestibulocochlear nerve or the central processing centres of the brain. In contrast, conductive hearing loss results from a defect in sound transmission through the external ear, tympanic membrane or middle ear.

In 1958, Lehnhardt first described an ‘antigen–antibody reaction’ in 13 patients with progressive bilateral SNHL. In his report, nine patients developed subsequent involvement of the contralateral ear, suggesting the possibility that an injury on one side sensitized the body to a cochlear antigen leading to hearing loss in the opposite ear [1]. In 1979, McCabe [2] describes one patient from a series of 18 with idiopathic bilateral progressive SNHL responsive to steroids, proposing the term autoimmune SNHL. This condition is also known as autoimmune inner ear disease (AIED), autoimmune cochleopathy or immune-mediated cochleovestibular disease [3, 4].

AIED accounts for fewer than 1% of all cases of hearing loss; however, this could be an underestimation based on the absence of specific diagnostic tests [3]. AIED is one of the few forms of sensorineural deafness that can potentially be treated.

Herein, we summarize the evidence on the pathophysiology and current approach to the diagnosis and treatment of adults with bilateral, progressive, fluctuating hearing loss. These data derive from a systematic review of the literature conducted in MEDLINE (1996 to October 2012) and EMBASE (1996 to October 2012). The search strategy included the terms autoimmune and hearing loss both as medical subject heading and keywords.

Definitions

In the absence of a reliable marker for AIED, the disease is defined by an appropriate clinical presentation, by exclusion of other known causes of SNHL and by a positive response to steroid therapy.

McCabe’s original description states that the time course of the hearing loss is the best clue to AIED diagnosis: ‘a period of progression of the deafness over weeks or months, not hours nor days nor years’ [2]. This course distinguishes AIED from sudden deafness and from age-related hearing loss (i.e. presbycusis). AIED is defined as primary when the pathology is restricted to the ear. In up to a third of cases, AIED occurs in the context of a
TABLE 1 Systemic autoimmune diseases associated with AIED

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Vogt-Koyanagi-Harada syndrome</td>
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<tr>
<td>Cogan’s syndrome</td>
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<td>Susac’s syndrome</td>
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<td>SLE</td>
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<tr>
<td>Antiphospholipid syndrome</td>
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<td>RA</td>
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<td>Systemic vasculitis</td>
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<td>Panarteritis nodosa</td>
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<td>Granulomatosis with polyangiitis</td>
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<td>SSc</td>
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<tr>
<td>Goodpasture syndrome</td>
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<tr>
<td>Behçet’s disease</td>
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<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>SS</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
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<tr>
<td>Polymyositis-dermatomyositis</td>
</tr>
<tr>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>AS</td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
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<tr>
<td>Multiple sclerosis</td>
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systemic autoimmune disease and is defined as secondary [5]. Table 1 provides a list of the systemic autoimmune diseases associated with AIED; the true frequency and the risk factors for developing AIED in the context of systemic autoimmune diseases are unknown.

Although there are no uniformly accepted criteria to diagnose AIED, the presence of bilateral SNHL of 30 dB or more at any frequency with evidence of progression in at least one ear on two serial audiograms performed less than 3 months apart is often used for case definition [6, 7].

Pathophysiology

The pathogenesis of bilateral, progressive, fluctuating hearing loss is unknown and therefore this represents one of the most controversial and challenging diseases in otology [8]. Since diagnostic biopsy of the human inner ear is not feasible, animal models are of major relevance in studying the aetiopathogenesis of this disease.

Viral infections or vascular disorders leading to cochlear or cochlear nerve damage have been postulated as mechanisms in bilateral, progressive, fluctuating hearing loss. However, up to date, there is very limited evidence to support the pathogenetic role of viral or vascular injuries [8].

The strongest pathogenic evidence is that of an immune-mediated disease. The inner ear is not an immunologically privileged site and may mount an immune response against foreign and self-antigens damaging sensory structures within it [9–11]. Both humoral and cell-mediated mechanisms are involved in the autoimmune injury to the inner ear. Cochlear innate immunity has been proposed to contribute to the initiation of a local adaptive immune response following antigen challenge. Briefly, as a consequence of a yet undefined trigger (i.e. antibody cross-reactivity, viral injury, trauma, vascular insult, surgical damage and others) damaging the inner ear, lymphocytes from the systemic circulation are exposed to proteins of the cochlea. Animals immunized with inner ear homogenate (reviewed in [12]) develop an immune reaction in the endolymphatic sac, which is a critical organ in processing and modulating immunity in the inner ear [13, 14]. Immune cells from the systemic circulation penetrate the blood-labyrinthine barrier to reach the endolymphatic sac [3]. Specifically, the blood vessels of the spiral modiolar vein adjacent to the scala tympani seem to be the initial site for lymphocyte entry to the inner ear [15]. Chronic activation of helper T lymphocytes reactive against self-proteins leads to the destruction of sensory and supporting cells within the cochlea. IL-1α, IL-2, TNF-α and NF-κB, cytokines essential in the initiation, modulation and amplification of the immune response, are expressed by infiltrating cells in the endolymphatic sac [16, 17]. The pathogenic role of autoreactive T-cell lines has been demonstrated by their passive transfer to naïve animals resulting in an inner ear autoimmune response [18, 19]. Thus, a critical task is to identify the inner ear antigens that trigger this autoreactive response. A proposed candidate is recombinant mouse cochlin, an extracellular matrix protein highly and specifically expressed in the inner ear [20]. When challenged with cochlin antigen, mice have robust T-cell proliferative responses, increased production of IFN-γ and cochlear inflammation [21]. Moreover, this form of primary AIED could be passively transferred into naïve recipient mice by CD4+ T cells. Of relevance, elevated levels of cochlin antibodies and increased frequencies of cochlin-specific IFN-γ-producing T cells have been found in patients with AIED [22, 23]. These studies provide evidence implicating an adaptive immune response, against an inner-ear-specific target antigen, with AIED. They also provide experimental confirmation that AIED may be a T-cell-mediated organ-specific autoimmune disorder of the inner ear [21]. Further data supporting the role of T cells in AIED derives from a murine study treated with adipose-derived mesenchymal stromal cells. This cell-based therapeutic strategy significantly improved hearing function via the down regulation of T-cell responses and the suppression of Th1/Th17-type cytokines through the generation of IL-10-secreting T-reg cells [24].

Circulating antibodies against a number of inner ear antigens leading to cytotoxic antibody-mediated damage (type II response) or immune complex-mediated damage (type III response) have been implicated in the pathogenesis of hearing loss in animal models. Sera from ~70% of patients with bilateral SSHL of unknown aetiology contain antibodies capable of immunostaining human inner ear tissues. Autoantibodies against type II collagen, type IX collagen, Raf-1 protein, the major peripheral myelin protein P0, B-actin, cochlin, choline transporter-like
protein 2 (CTL2), cell-density enhanced protein tyrosine phosphatase-1 and connexin 26 have all been described in AIED [4, 25, 26]. The stria vascularis, fibrocytes of the spiral ligament and supporting cells are the anatomical targets of those autoantibodies.

Harris and Sharp [27] were the first to show that western blots of serum from patients with AIED had an antibody directed against the 68-kDa inner ear antigen characterized as a heat shock protein (HSP70) found in the inner ear. Of relevance, elevated HSP70 antibodies are not the underlying cause of hearing loss but rather a non-pathogenetic epiphenomenon [28, 29]. However, antibodies to HSP70 are found in AIED patients and their presence was correlated with responsiveness to steroid treatment [6]. The sensitivity and specificity of anti-HSP70 for the diagnosis of AIED was 42% and 90%, respectively, and their positive predictive value 91% [30].

In experimental models of AIED (i.e. the immunization of a guinea pig with swine inner ear antigens in complete Freund’s adjuvant), it is possible to induce cochlear dysfunction, endolympathic hydrops and development of antibodies to 68-, 50-, 45- and 27-kDa molecular weight inner antigens. The target antigen seems to be a choline transporter-like protein 2 (CTL2), a member of the choline transporter-like protein family linked to acetylcholine synthesis, which is an inner ear glycoprotein of 68 and 72 kDa [31].

In summary, both arms of the immune system, innate and adaptive, are implicated in the processes ultimately leading to the histopathological features in the cochlea of patients with AIED. Those include damage to the organ of Corti, retrograde neural degeneration to the level of the spiral ganglion, endolympathic hydrops, stria vascularis dystrophy, neo-fibroosteogenesis in the basal turn of the cochlea, fibrosis of the endolympathic sac and lymphocytes in the labyrinthine membrane compartment [32–35].

Clinical manifestations

AIED most commonly affects people in the third to sixth decades of life and presents with unilateral or bilateral SNHL that progresses over several weeks to months [2, 36]. This time course of the hearing loss is the best clue to the diagnosis. Although at presentation 50% of patients report unilateral hearing loss, audiological evaluation demonstrates asymmetrical but bilateral involvement in the vast majority of cases (80–100%) [2]. Fluctuations in hearing are common but the overall course is one of progressive deterioration of auditory function [37–39].

Vestibular symptoms such as generalized imbalance, motion intolerance, ataxia and positional or episodic low-grade vertigo are present in 50–80% of patients [3, 35, 37]; 25–50% have tinnitus and aural fullness meeting criteria for Menière’s disease [37]. In fact, during the first months, the differential diagnosis between Menière’s disease and AIED can be difficult. The more aggressive course of AIED will allow the differentiation. Moreover, some forms of bilateral Menière’s disease seem to have an underlying autoimmune pathology [40]. Some authors suggest that any patient diagnosed with unilateral Menière’s disease who develops symptoms in the contralateral ear should undergo workup for an autoimmune aetiology [37]. As stated earlier, up to a third of AIED cases occur in the context of a systemic autoimmune disease, and unusually can be the first manifestation of the latter.

Diagnosis

Essentially all patients with AIED initially present to and are evaluated by otorhinolaryngologists who often consult rheumatologists to rule out an underlying systemic autoimmune disease or to assist in monitoring the immunosuppressive therapy. The following features should be determined from the history in any patient presenting with hearing loss: (i) length of time over which the hearing loss has developed, (ii) associated otological symptoms (tinnitus, vertigo, pain, discharge and pressure) and (iii) predisposing factors (i.e. noise exposure, chemotherapy or antibiotic treatments, previous ear surgery, trauma, meningitis or family history of hearing loss). Differentiating between AIED and sudden hearing loss is critical. Although at the initial presentation AIED may be more evident in one ear, it progresses over weeks to months, involving both ears. In contrast, sudden hearing loss is unilateral and develops in 72 h or less. In addition to the specific otological history, it is relevant to perform a complete review of systems since in 15–30% of cases patients with AIED have or will develop a systemic autoimmune disease (Table 1) [36]. Thus, the presence of recurrent or chronic ocular disease, nephritis, arthritis, pneumonitis, sinusitis, photosensitivity and symptoms suggestive of inflammatory bowel should be established. In addition to causing SNHL, autoimmune diseases can lead to conductive hearing impairment. In fact, up to a third of patients with granulomatosis with polyangiitis have conductive hearing loss secondary to effusions from granulomatous involvement of the middle ear and eustachian tube mucosa [41]. Similarly, eustachian tube dysfunction is not uncommon in patients with relapsing polychondritis [42], while the ossicular chain can be affected by RA, leading to conductive hearing loss in more than 15% of RA patients [43].

Therefore, the first step in the evaluation of a patient presenting with hypoacusia is to define whether the hearing loss is sensorineural or conductive. This is based on the physical examination, specifically on the otoscopy findings and tuning forks tests. The magnitude of hearing loss is then defined by an audiogram where air and bone conduction hearing thresholds are quantified and compared. Fig. 2 shows a representative example of an audiogram of conductive hearing loss and SNHL. The audiological assessment is a crucial part of both the initial diagnostic evaluation and all subsequent follow-ups of patients with hearing loss, allowing the characterization of the severity, frequencies involved and symmetry. The most important components of the audiological assessment in patients with AIED are (i) pure-tone air conduction threshold testing, the goal of which is to obtain a representation of the softest intensity heard across frequencies (0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz) comparing
observed threshold with normative data [pure-tone average (PTA) is the arithmetical average of thresholds] and (ii) word discrimination, which probes the ability to perceive, process and verbally reproduce phonological units that comprise spoken words. Speech discrimination score/word intelligibility score (WIS) is the percentage of words a patient can repeat at a comfortable listening level. A WIS of 70% or more is considered indicative of good potential for spoken communication. So maintaining or reaching a WIS of 70% is a good clinical outcome. Table 2 summarizes the functional impact of different degrees of hearing impairment.

The next relevant step is to exclude other disorders that can mimic AIED (i.e. multiple sclerosis, malignancies and otosyphilis) [36]. Based on expert opinion, the recommended routine serology tests in patients with AIED include complete blood count, ESR, RF, ANA test, anti-dsDNA antibodies, anti-SSA/B antibodies, antiphospholipid Abs, HIV, fluorescent treponemal Ab absorption test [30, 44, 45]. In the absence of symptoms and signs of autoimmune diseases, the value of including serology testing appears limited [46, 47]. Moreover, positive results of those tests are not predictive of improvement following steroid treatment [39]. Serology studies for viral infections are not recommended in AIED [48].

If the cause of the hearing loss is not identified, particularly in patients with asymmetric SNHL, an MRI should be ordered to rule out retrocochlear pathologies such as acoustic neuroma, intracranial metastases, demyelinating or ischemic diseases. AIED is suspected when no clear aetiology is found in the imaging studies, and there is progression of the documented SNHL that is too slow to be a sudden SNHL (which is unilateral and defined as developing over 72 h), but too fast to be presbycusis (which develops over many years).

Despite significant efforts, to date there are no reliable diagnostic tests for AIED. Lymphocyte migration inhibition assays and lymphocyte transformation tests have initially been included as part of the diagnostic approach; however, their diagnostic accuracy remains undetermined. The use of the enzyme-linked immunospot (ELISPOT) assay to assess the frequencies of peripheral blood T cells capable of producing IFN-γ in response to homogenates of human inner ear tissue in patients with AIED was tested in a small study including 12 patients. This study showed that 25% of AIED patients have increased frequencies of inner-ear-specific IFN-γ-producing T cells in peripheral blood [23, 49]. Similarly to cellular assays, serological tests to detect antibodies against inner ear antigens lack sufficient specificity to be used as diagnostic tools [50]. The OtoBlot assay, a commercially available western blot assay for anti-hsp70 antibodies, has low sensitivity (50%) [29, 47, 51, 52]. More recently, anti-CTL-2 antibodies were demonstrated in 50% of AIED sera; however, this test is not commercially available and its
The usefulness of PET for assessing active disease is controversial [54, 55].

**Treatment**

A multidisciplinary team that includes an otolaryngologist, a rheumatologist and an audiologist should treat a patient with AIED, monitor therapeutic responses and prevent side effects associated with immunosuppressants. Patients with AIED should be followed with audiograms on a monthly basis until their hearing stabilizes, and every 6 months thereafter unless changes in the hearing capacity occur. A significant change in hearing is defined by any of the following criteria: a threshold shift of 15 dB or more in one frequency; a threshold shift of 10 dB or more at two or more consecutive frequencies; 10 dB or more change in PTA [37, 56–59]; 12–20% or above change in discrimination score at 40 dB sensation level [7, 60, 61]. In addition, to be considered as improvement in hearing, some authors will request no additional threshold loss at any other frequency and no additional loss in discrimination in either of the ears [52].

**Steroids**

Corticosteroid therapy is the mainstay of AIED treatment due to its immunosuppressive properties and its effects on the modulation of sodium transport. There are no prospective randomized clinical trials on which to base the dose, route and length of the corticosteroid treatment. Moreover, although many patients have short-term response to steroids, the response is generally not sustained [62].

The most widely used regimen by otologists is an empiric treatment protocol proposed by Rauch et al. [7] based on 150 patients in whom autoimmune inner disease was clinically suspected. Initial therapy in adults is a 60 mg/day or 1 mg/kg/day therapeutic trial of prednisone for 4 weeks. Patients’ hearing is tested at the initiation of therapy and 1 month later. A response is documented at the end of 4 weeks in 50–70% of cases [38] and those patients continue therapy until monthly audiograms demonstrate stabilization [63]. At that point, steroids are tapered over 8 weeks to a maintenance dose of 10 mg for a total treatment

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**TABLE 2** Scales of hearing impairment and their functional implications based on PTA and speech discrimination score (SDS)

<table>
<thead>
<tr>
<th>PTA (dB)</th>
<th>Degree of impairment</th>
<th>Functional implication in terms of need for hearing aid and lipreading</th>
</tr>
</thead>
<tbody>
<tr>
<td>−10 to 15</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>16–25</td>
<td>Slight</td>
<td>Possibly</td>
</tr>
<tr>
<td>26–40</td>
<td>Mild</td>
<td>Probably</td>
</tr>
<tr>
<td>41–65</td>
<td>Moderate</td>
<td>Definitely</td>
</tr>
<tr>
<td>66–95</td>
<td>Severe</td>
<td>Definitely</td>
</tr>
<tr>
<td>&gt;95</td>
<td>Profound</td>
<td>Definitely</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SDS (%)</th>
<th>Degree of impairment</th>
<th>Functional implication on conversational abilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>90–100</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>75–90</td>
<td>Mild</td>
<td>Slight, comparable to a conversation over the phone</td>
</tr>
<tr>
<td>60–75</td>
<td>Moderate</td>
<td>Moderate difficulty</td>
</tr>
<tr>
<td>50–60</td>
<td>Severe</td>
<td>Marked difficulty in following a conversation</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Profound</td>
<td>Unable to follow running speech</td>
</tr>
</tbody>
</table>

Adapted from Semin Arthritis Rheum 2004;34:538–43, with permission from Elsevier.
of at least 6 months. Relapses that are associated with treatment duration of less than 6 months require escalation of the dosage until stabilization is achieved. In patients who fail to respond to the initial 4-week trial, steroids are tapered over 12 days.

Steroid-associated adverse effects occur in 15% of AIED patients during the first month of treatment and 6% have to discontinue steroid therapy [56]. Several strategies have been proposed to overcome this problem. Some authors have suggested the use of shorter steroid regimens [38]; however, those might be associated with higher rate of relapse [3]. The use of systemic mineralocorticoids (aldosterone and fludrocortisone) alone or in combination with glucocorticoids seems to be useful in animal models but has not been tested in humans [64, 65]. Intratympanic steroid injections have been tested in AIED patients refractory to steroids [66]. Despite high penetration of transtympanic methylprednisolone into the cochlear fluids [67], the evidence supporting its use in AIED is limited. In a small retrospective case series of 11 patients, transtympanic 6-methylprednisolone was safe and useful. Those patients received weekly injections of 6-methylprednisolone (0.3–0.5 ml, 40 mg MP/ml) for 2 months and 54% of them had hearing improvement with significant reduction of the vestibular symptoms [66]. Some patients prefer to avoid or cannot tolerate the side effects of steroid therapy and in those cases consideration may eventually need to be given to cochlear implants if the patient deteriorates to profound hearing loss.

Non-steroidal immunosuppressants

A significant number of patients with AIED have primary or secondary response failure to steroids, are steroid dependent or experience unacceptable side effects. In these patients, alternative immunosuppressive approaches and steroid-sparing agents are required. Cyclophosphamide appears to be an effective therapy and its use in association with steroids was first described in McCabe’s series [2]. However, the extended follow-up of patients treated with cyclophosphamide for other benign conditions has been associated with a high incidence of serious drug-related toxicities prompting the search for other immunosuppressive options. The evidence supporting the use of ciclosporin A [57], MMF [37, 58] and AZA [37, 60] in AIED is based on case reports and small case series and not conclusive. We will discuss agents for which stronger evidence is available.

**Methotrexate**

(MTX 7.5–25 mg/week) has been used as a prednisone-sparing treatment for refractory autoimmune hearing loss or as an adjunct to maintain or further improve the symptoms. Non-randomized studies including a prospective observational study of 53 patients demonstrated good tolerance and an overall 70% response rate with vertigo improving in 69%, hearing loss in 53% and tinnitus in 26% [68]. Moreover, in that study, most patients were able to stop therapy after 1–2 years without recurrence of symptoms [68]. In another prospective 12-month open-label study including 17 patients with refractory autoimmune hearing loss, MTX treatment was associated with hearing improvement in 65% of the cases, stabilization in 23% and worsening in 12% [69]. A discrepancy between rates of improvement based on audiometric parameters (65%) and on patient’s perception (35%) was evidenced in this study raising the issue of using the latter as a relevant outcome for future intervention studies [69].

In 2003, the only prospective, multicentre, randomized, double-blind, placebo-controlled trial in AIED was reported. This trial was designed to assess the efficacy of long-term MTX (52 weeks, MTX dose: 15 mg/week) in the maintenance of initial hearing improvement in response to prednisone therapy in patients with primary AIED. The study included 67 patients and was terminated early due to no apparent benefit of MTX over placebo in maintaining clinical response during prednisone tapering [61]. However, this study did not assess the impact of MTX on vestibular symptoms nor hearing fluctuations over time, which previous MTX open-label studies reported to improve [66].

**Biologics**

Almost every biologic agent has been used for the treatment of AIED. Most of the available evidence on these agents derives from observational studies, case reports and case series, which can be confounded by selection and publication bias. There are no randomized clinical trials assessing the effectiveness of the use of specific biologics in AIED.

**Cytokine modulation**

Blocking TNF-α, both systemically and locally, has shown promising results in models of AIED [70]. In animals, the efficacy of etanercept was similar to that of glucocorticoids as a primary treatment modality [71]. In humans, TNF-α blockers have been used in refractory cases but not as a first line of therapy. Overall, the available evidence failed to demonstrate a significant effect of anti-TNF agents on hearing outcomes in these patients.

A retrospective case series of 12 patients with AIED who did not respond to conventional stabilization therapies but showed initial response to high-dose prednisone, or who experienced side effects with conventional therapy, were treated with etanercept 25 mg s.c. twice weekly for 6 months. Improvement or stabilization of hearing and tinnitus was observed in 92% of the patients [72]. In addition, seven of eight patients who had vertigo (88%) and eight of nine patients who had aural fullness (89%) had resolution or significant improvement of their symptoms. In contrast to these results, an open-label prospective pilot study of 23 patients with bilateral immune-mediated cochleovestibular disorders treated with etanercept for 24 weeks (25 mg subcutaneously twice weekly) did not suggest substantial efficacy, with only 30% of patients showing improvement in audiometric criteria [55]. In this study, hearing did not change in
57% of patients, leaving unanswered the question of whether etanercept might have a role in disease stabilization when steroid treatment is inadequate. Subsequently, a randomized controlled pilot trial involving 20 patients with AIED showed that treatment with etanercept 25 mg twice weekly over 8 weeks was no better than placebo in improving hearing [73]. The drawbacks of this study were the small sample size, length of treatment and the inclusion of a heterogeneous patient population with variable disease duration with multiple previous treatments.

A recent retrospective review of eight patients with suspected autoimmune hearing loss refractory to all standard treatments treated with infliximab failed to document positive therapeutic responses based on objective hearing measurements [74]. Since antibodies have been demonstrated to cross the round window membrane [75, 76] and since TNF-α blockers were not found to be ototoxic, transtympanic infliximab administration was tested [77]. In a prospective pilot study nine patients diagnosed with AIED with initial response to oral steroids were treated with 0.3 ml of infliximab once weekly for 4 weeks through a transtympanic tube and a MicroWick. Response defined as improvement in hearing loss with steroid tapering was associated with a reduction in the relapse rate was observed in seven patients [77].

A single case suggesting the benefit of adalimumab in conjunction with MTX for the control of AIED [59] was challenged by two reports of de novo AIED associated with this monoclonal antibody [78].

A recent study evaluating the pathways that control corticosteroid responsiveness in 47 patients with AIED has shown that increased levels of IL-1β expression are associated with corticosteroid resistance, suggesting a role for IL-1β inhibition in clinical corticosteroid non-responders [79].

Cell modulation

Rituximab (anti-CD20 mAb) was tested in an open-label study of seven patients with primary immune-mediated inner steroid-responsive AIED. A course of rituximab (1000 mg i.v. for two doses 2 weeks apart) prior to starting prednisone tapering was associated with sustained response (evaluated at week 24) following steroid discontinuation in five out of seven patients (24-week follow-up) [80]. The results of this pilot study support the evaluation of rituximab in a properly designed randomized clinical trial [80].

In summary, the current evidence supporting the use of steroid-sparing agents among them biologic agents as a treatment for AIED is still anecdotal. Properly designed randomized controlled trials are necessary to establish the efficacy of biologics as the treatment of AIED. Given the high cost of these agents, if efficacy is proven, cost-effectiveness studies comparing them to the alternative of a cochlear implant will certainly be warranted before they become part of the standard treatment.

Plasmapheresis

The benefit of plasmapheresis (PMP) for AIED was evaluated in studies including small number of patients (8–21 patients). Luetje et al. evaluated the long-term hearing outcome in 16 patients who had tried other treatments without success and received PMP on alternate days for cycles of three exchanges. The average follow-up of these patients was 7 years. The authors suggest that 39% of the ears met the criteria for hearing improvement or stability and 25% of the patients required continuing immunosuppressive drugs [81]. The precise role of PMP in AIED and its relation to immune suppression needs to be defined.

Cochlear implantation

The subset of patients with AIED who develop profound irreversible bilateral SNHL who no longer benefit from hearing aid amplification become candidates for cochlear implantation [82]. Outcome studies have demonstrated excellent results and performance above average in implanted AIED patients, compared with patients with other causes of deafness [82–84].

Conclusion

The absence of reliable markers for AIED has forced clinicians to define the disease based on its clinical presentation, exclusion of other known causes, and a positive response to steroid therapy. In every patient who has progressive bilateral SNHL with no other explainable cause, the diagnosis of AIED should be considered, the association with a systemic autoimmune disease evaluated and a trial of corticosteroids attempted.

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Autoimmune inner ear disease

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