Otology seminar: Autoimmune inner ear disorder (AIED)

R3 陳贈成

■ Introduction
- In 1958, Lehnhardt was the first to postulate autoimmune process against the inner ear.
- In 1979 McCabe reported 18 cases of SNHL and introduced the clinical entity of autoimmune-mediated SNHL.
  ➢ Positive lymphocyte inhibition test
  ➢ Substantial hearing improvement with steroid Tx
  ➢ Histopathologic exam. : vasculitis
- In 1990, Orozco et al., animals immunized with inner ear proteins ➔ modest, transient HL, cochlear inflammation.

■ Pathogenesis
- Inner ear: an immunoprivileged site, protected by the blood-labyrinthine barrier.
- Immune response in inner ear: dependent on an intact endolymphatic sac (ES).
- Develop in the ES and from systemic circulation penetrating the BBB
  ➢ Antigen processing

Fig. 1. Effect of obliteration of the endolymphatic sac on an inner ear immune response. The endolymphatic sac of guinea pigs was surgically ablated. Systemic immunization with keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA) was then followed by inner ear challenge with KLH. Perilymph anti-KLH antibody levels resulting from the challenge, indicative of an active inner ear immune response, were significantly reduced in inner ears without an endolymphatic sac. Anti-BSA antibodies, indicative of passive filtration from serum, were unaffected. Adapted from Tomiyama and Harris (17).

- Sac: the only inner ear which reside lymphocyte, release mediator
- enter the scala tympani via the spiral modiolar vein
- T helper (CD4) cell: predominate; CD8 cells: scanty ➔ reverse after stimulation
- IL-2: peak rise in perilymph after 18h following antigen stimulation, declined over a 5-day period.
- Two theory: **cross-reaction theory** and **sympathetic cochleolabyrinthitis**
- Possible anatomical targets of auto-Abs in Primary AIED:
  - vasculce
  - fibrocytes of spiral ligament
  - supporting cells, Type II collagen (MD, Otosclerosis, SD), evidence ↑
- Sympathetic hearing loss: anatomically sequestered proteins in inner ear
  - 68-72kDa inner ear antigen; HSP-70, choline transporter-like protein 2 (CTL2)
    - Choline: biosynthesis of acetulcholine, inner ear neurotransmitter
      - Phosphatidylcholine: major component of membrane
  - Cochlear outer hair cell
- **Stria vascularis pathology** (from MRL-Fas<sup>lpr</sup> mouse model)
  - Only site of pathology in AIED mice; no hair cell pathology
  - Glucocorticoid function: immune suppression, anti-inflammation and sodium reabsorption
  - No direct evidence of inflammatory processes in the mouse ear
  - Glucocorticoid: increase membrane Na<sup>+</sup> channels
  - Mineralocorticoid: upregulate mRNAs ➔ Na<sup>+</sup>,K<sup>+</sup>-ATPase elevation
Preexisting hearing loss might predispose to sympathetic hearing loss

- Incidence: can not be determined; more common in female, peak 20~50 y/o
- **Clinical presentation**
  - Too rapidly for presbycusis, too slowly for SD
  - Progressive, fluctuating, bilateral SNHL, responds to steroid Tx, closely mimic Meniere’s disease
  - Vestibular symptoms, 50%
  - Bilateral and asymmetric, over weeks to months
  - SNHL most occur in the low and mid-frequencies; High tone SNHL: more common when vasculitis is suggested etiology
  - Tinnitus and aural fullness, 25~50%
  - Systemic autoimmune disease coexist in 15~30% of patients

- **Proposed disease-specific antibodies**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular mass (kDa)</th>
<th>Patient diagnosis</th>
<th>Antigen source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IX collagen</td>
<td>100</td>
<td>MD</td>
<td>Human</td>
<td>[16]</td>
</tr>
<tr>
<td>Type II collagen</td>
<td>96</td>
<td>ASNH, MD</td>
<td>Chick, human</td>
<td>[10,16]</td>
</tr>
<tr>
<td>KHR-3</td>
<td>68 – 72</td>
<td>– (rabbit antiserum)</td>
<td>Guinea pig</td>
<td>[21]**</td>
</tr>
<tr>
<td>Cochlin</td>
<td>58</td>
<td>ASNH, MD</td>
<td>Guinea pig, mouse</td>
<td>[9**,42]</td>
</tr>
<tr>
<td>β-Tectorin</td>
<td>36 – 43</td>
<td>– (mouse antiserum)</td>
<td>Mouse</td>
<td>[9**]</td>
</tr>
<tr>
<td>β-Actin</td>
<td>42 – 45</td>
<td>ASNH</td>
<td>Guinea pig</td>
<td>[12]</td>
</tr>
<tr>
<td>Myelin protein P0</td>
<td>30</td>
<td>ASNH, SHL, MD</td>
<td>Guinea pig</td>
<td>[14,37]</td>
</tr>
<tr>
<td>Rel-1</td>
<td>28</td>
<td>MD</td>
<td>Guinea pig</td>
<td>[13]</td>
</tr>
<tr>
<td>Connexin 26</td>
<td>25</td>
<td>Cogan’s syndrome</td>
<td>Random peptide library</td>
<td>[20]</td>
</tr>
</tbody>
</table>

DEP-1/CD148, cell-density enhanced protein tyrosine phosphatase-1; ASNH, autoimmune sensorineural hearing loss; MD, Meniere’s disease; SHL, sudden hearing loss; KHR-3, Kresge Hearing Research Institute-3.

- No specific commercially test for AIED now
- Migration inhibition test (MIT), Lymphocyte transformation test (LTT), Western blot analysis ➔ result controversial

- **Disease non-specific antibodies**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence (%)</th>
<th>Patient diagnosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibody (ANA)</td>
<td>18 – 43</td>
<td>ISNH, ASNH</td>
<td>[52,53,54**]</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibody (ANCA)</td>
<td>Case report</td>
<td>ASNH</td>
<td>[55]</td>
</tr>
<tr>
<td>Antibasemential cell antibody (AECA)</td>
<td>47 – 53</td>
<td>ISNH</td>
<td>[52,56]</td>
</tr>
<tr>
<td>Antiphospholipid/anticoagulon antibodies</td>
<td>58</td>
<td>ISNH</td>
<td>[54**]</td>
</tr>
<tr>
<td>Antithroid antibodies</td>
<td>22</td>
<td>ISNH</td>
<td>[54**]</td>
</tr>
<tr>
<td>Rheumatic factor</td>
<td>12</td>
<td>ISNH</td>
<td>[54**]</td>
</tr>
<tr>
<td>Heat shock protein 70</td>
<td>22 – 59</td>
<td>ASNH, MD</td>
<td>[7,46]</td>
</tr>
</tbody>
</table>

ISNH, idiopathic sudden sensorineural hearing loss ASNH, autoimmune sensorineural hearing loss MD, Meniere’s disease.

- ANA: for SLE sensitivity high, specificity low; 18-43% AIED (+)
- ANCA: associated with small vessel vasculitis, Wegener’s granulomatosis
- AECA: associated with immune-mediated vasculitis, 47-53% AIED (+)
- RF: for RA, very sensitive but poorly specific marker, 12-35% AIED (+)
- Antiphospholipid Ab: autoimmune disorder, infectious disease, neoplastic disorder,
healthy individual, 31% SD (+); 25% idiopathic progressive SNHL (+)
- Antithyroid Abs: 22% AIED (+)
- Another neurologic manifestation of the antiphospholipid syndrome: 25% aPL or aCL (+), microthrombus formation in the labyrinthine vasculature
- ANA: more useful than ESR, C3, C4 or Western blotting for Hsp 40
- Essential test: ANA, complete ENT examination, MRI, fluorescent treponemal Ab

**Diagnosis**
- *Absence of a golden standard criteria; History, History, History*
- Diagnostic biopsy of inner ear: not feasible, major obstacle

![Graph](image)

*Fig. 2. Reduction of virally-induced hearing loss by systemic immnosuppression. Inner ear injection of cytomegalovirus (CMV) in phosphate-buffered saline (PBS) resulted in ≈ 50 dB of hearing loss in guinea pigs, compared to <10 dB after injection of PBS alone. Treatment with cyclophosphamide (CYP) prior to viral challenge significantly reduced hearing loss. Adapted from Damsma et al. (32).*

- **Bilateral progressive involvement**, fails to respond to conventional medical treatment (low-salt diet, vestibular suppression, diuretics)
- **Audiometric and/or symptomatic improvement after a short course of high dose steroid** (1mg/kg/d for 2-4 weeks)

**Acute Profound Deafness Research Committee Criteria**

<table>
<thead>
<tr>
<th>Table 3 Tentative diagnostic criteria for probable immune-mediated sensori-neural hearing loss by the Acute Profound Deafness Research Committee of Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Hearing loss&lt;br&gt; (a) Hearing loss is responsive to administration of immunosuppressive agents, especially steroids&lt;br&gt; (b) The patient has symptoms described above under (a) and meets criteria (2) and/or (3) below</td>
</tr>
<tr>
<td>(2) The patient has an associated systemic immune-mediated disorder</td>
</tr>
<tr>
<td>(3) Positive results or abnormal values are obtained in any of the following tests&lt;br&gt; (a) Haematological&lt;br&gt; i. Erythrocyte sedimentation rate, or&lt;br&gt; ii. Red blood cell, white blood cell and platelet count&lt;br&gt; (b) Serological&lt;br&gt; i. Creatine protein&lt;br&gt; ii. Assay for serum proteins, IgG and IgM&lt;br&gt; iii. Syphilitic reaction&lt;br&gt; iv. Immune complexes, cryoglobulin&lt;br&gt; v. Rheumatic factor&lt;br&gt; vi. Tissue nonspecific antibodies with high disease specificity detected in patients with systemic autoimmune disease&lt;br&gt; (c) Others&lt;br&gt; i. Tolerant skin test&lt;br&gt; ii. Prolactina, haematuria</td>
</tr>
</tbody>
</table>


- Systemic history: recurrent or chronic ocular disease, nephritis, arthritis, pneumonitis, sinusitis, and inflammatory bowel disease
More specific laboratory testing for systemic disease is warranted when the ESR is elevated. General screening test: ANA, ESR, RA; antigen-specific test: HSP-70 western blot ……from Texas Southwestern Medical school study. The ERS, CRP: acute phase detector. Specific immunological test batteries:
- CBC/DC
- ANA, Anti-ds DNA
- anti-SSA/B Ab
- antiphospholipid/anticardolipin Ab
- C3 and C4 complement, Raji cell
- VDRL
- MRI with enhancement: rule out retrocochlear lesions
- ECoG: almost 50% had evidence of Endolymphatic hydrops (SP/AP>0.37)
  - Rauch et al, 1995: Meniere’s disease, 47% Hsp 70 (+), especially bilateral involved
  - Hughes etal, 1988: 50% AIED patient fit the criteria of Meniere’s disease
  - Unilateral Meniere’s disease, contralateral develops new symptoms

work-up for autoimmune etiology
- Serial limited PET of inner ear

### Treatment:
- treatment options are limited
- **Steroid:** the only validated treatment option, standardized regimen dose not exist, 1mg/kg/day for 4 weeks; shorter-term or lower dose long term: ineffective or increase the risk of relapse
  - Hughes et al, improvement 40%, stable 45%, decreased 15%

### Table II. Costs of the tests included in the previous study [2].

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost (€)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>18.08</td>
</tr>
<tr>
<td>ESR</td>
<td>15.60</td>
</tr>
<tr>
<td>ANA</td>
<td>22.55</td>
</tr>
<tr>
<td>IgA, IgG, IgM</td>
<td>16.54</td>
</tr>
<tr>
<td>Western Blot for HSP 70</td>
<td>41.47</td>
</tr>
<tr>
<td>Immunophenotype of PBL</td>
<td>30.56</td>
</tr>
<tr>
<td>Complement factors C3 and C4</td>
<td>41.35</td>
</tr>
<tr>
<td>FTA</td>
<td>55.60</td>
</tr>
<tr>
<td>Audiogram</td>
<td>90.22</td>
</tr>
<tr>
<td>MRI</td>
<td>670.69</td>
</tr>
<tr>
<td>Total cost</td>
<td>1008.66</td>
</tr>
</tbody>
</table>

*1€ = 1.29 USD as of April 25.

### Table I. Comparative analysis of steroid responsive subgroups of patients considering the diverse criteria used for the immunologic study.

<table>
<thead>
<tr>
<th>Group</th>
<th>ANA titer</th>
<th>CD4/CD8RA</th>
<th>Systemic autoimmune disease</th>
<th>HSP 70</th>
<th>Blunted ESR</th>
<th>IMIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous study [2] (n=8)</td>
<td>15 (33.3)</td>
<td>26 (57.7)</td>
<td>4 (8.8)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>26</td>
</tr>
<tr>
<td>This study (n=21)</td>
<td>10 (53)</td>
<td>8 (46)</td>
<td>5 (27)</td>
<td>NP</td>
<td>NP</td>
<td>11</td>
</tr>
<tr>
<td>Previous study [2] (n=8)</td>
<td>4 (50)</td>
<td>3 (37.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4</td>
</tr>
<tr>
<td>This study (n=9)</td>
<td>2 (22.2)</td>
<td>2 (22.2)</td>
<td>1 (11.1)</td>
<td>NP</td>
<td>NP</td>
<td>2</td>
</tr>
<tr>
<td>Previous study [2] (n=8)</td>
<td>1 (12.5)</td>
<td>2 (25)</td>
<td>0 (0)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>This study (n=9)</td>
<td>1 (11.1)</td>
<td>3 (33.3)</td>
<td>1 (11.1)</td>
<td>NP</td>
<td>NP</td>
<td>2</td>
</tr>
</tbody>
</table>

NP = not performed.
- Response(+), tapered more slowly over one month; Response(-), tapered off over a week to 10 days
- If recur during the taper, repeat the initial high dose treatment
- Sensitive predictor of relapse: moderate to severe tinnitus in one or both ears
- No response to steroids within 6~8 weeks of can’t weaned without relapse: addition of cytotoxic drug, often are methotrexate (MTX) or Cyclophosphamide
- When dealing with cytotoxic drugs ➔ Rheumatologist, Immunologist, Haematologist, Ophthalmologist, Neurologist should be consulted ➔ to rule out systemic disease
- Multidisciplinary decision should be made

- **Methotrexate:** 7.5~20mg weekly with folic acid
  - Sismains et al, 1994, Laryngoscope: 5 AIED P’t, objective data not improved…??
  - follow up CBC, BUN, Cr, GOT, GPT, urinalysis
  - Harris et al, 2003, JAMA: no more effective in maintaining hearing improvement in patients with AIED

- **Cyclophosphamide:** when refractory to steroid, side effect ↑
  - McCabe advocated as a first line drug
- **Azathioprine**: 1mg/kg once daily with prednisolone 30mg daily for 4 weeks
  - Saracadin A, et al, 1993: 10/12 patients experienced statistically significant improved

- **Transtympanic steroid Tx**: not encouraging
  - Yang GS, et al, 2000: Local application of immunosuppressives did not suppress inner ear inflammatory infiltrates and hearing loss
  - Jackson LE, et al, 2002: AIED treated with MicroWick, case number too small, result inconclusive

- **Anti- Interstitial cell adhesion molecule-1 (ICAM-1)**: on the activated endothelial cells for lymphocyte recruit
  
  ![Graph showing reduction of immune-mediated infiltration of leukocytes into the inner ear by intravenous anti-ICAM antibodies.](image)

  *Fig. 4. Reduction of immune-mediated infiltration of leukocytes into the inner ear by intravenous anti-ICAM antibodies. Keyhole limpet hemocyanin (KLH) challenge of the inner ears of sensitized guinea pigs resulted in significantly more inflammatory cells in the cochlear perivascular spaces (PVS), scala tympani (ST) and VIIIth nerve (VIIIth N) than were observed after phosphate-buffered saline (PBS) challenge. However, intravenous anti-ICAM-1 antibody treatment prior to labyrinthine challenge significantly reduced the leukocytic infiltration of the inner ear. Adapted from Tarsa and Harris (41).*

- **Cochlear implant**: for severe to profound hearing loss

- **Aldosterone Treatment** (Autoimmune mouse ear model. MRL/MPJ-Fas<sup>Irpr</sup>)
Underlying pathology in the ear:

- Better (> 20dB)
- Unchanged (±15 dB)
- Worse (> 20dB)

**Graph 1:**
- X² = 5.3, p = 0.07
- X² = 2.6, p = 0.25
- X² = 2.1, p = 0.34
- X² = 0.4, p = 0.80

**Graph 2:**
- Baseline
- 4 Months Tg

**Graph 3:**
- Mineralocorticoid
- Glucocorticoid

Glucocorticoids have strong binding affinity for both receptors

- Ion Homeostasis:
  - Na⁺, Ca²⁺, and K⁺ channels
  - Na⁺,K⁺-ATPase
  - Na⁺/Cl⁻ cotransporter

- Immune System:
  - Lymphocytes
  - Macrophages
  - Inflammatory cytokines

- Regulate endolymph homeostasis
- Suppress autoimmune disease & inflammation
not reversed with glucocorticoid-receptor mediated process
mineralocorticoid-related processes on stria vascularis and spiral ligament

- **Plasmapheresis:**
  - Luetje and Berliner, 1989, six of eight patients effective
  - Expensive, only suitable for antibodies or immune complex disorder
  - Three times weekly for two weeks ➔ one weekly for 4 additional weeks

■ **Prognosis**
- Recovery rates ranging from 47% to 63% (partial and complete recovery)

■ **Conclusion**
- No uniform criteria for diagnosis
- Evidence-based diagnostic criteria and assessment tools: remain a challenge
- *Autoimmune inner ear disease (steroid responsive hearing loss)* ➔ *may need to revised*

■ **Reference**


