Otology seminar

Autoimmune inner ear disease

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Purpose

- Extremely important
  - one of the few medically reversible SNHL
- Summarize basic science research about pathogenesis
- Review the current diagnostic work-up
- Delineate treatment strategies
Immune system of Inner Ear

- Blood-labyrinthine barrier → immunoprivileged
- Perilymph includes immunoglobulins (IgG, lesser IgM, IgA), 1/1000 of serum
- The endolymphatic sac plays a significant role
  - T helper (CD4) cells predominate
  - Tomiyama and Harris: perilymph antibody and cellular infiltrates in the cochlea reduced after the obliteration of the ELS
Background

- Lehnhardt in 1958: first to postulate autoimmune process → sudden or bilateral HL
  - One ear initially (9/13) → degeneration of the organ of Corti → anti-cochlear antibodies damaged the other ear
- McCabe in 1979: 18 cases
  - Idiopathic SNHL over weeks to months
  - Response to oral steroid
  - Tinnitus, aural fullness, unsteadiness or ataxia
  - Positive lymphocyte inhibition assay (6/6: +)
Background

- Yoo in 1984: type II collagen, degeneration of spiral ganglion cells, atrophy of cochlea nerve, organ of Corti, and stria vascularis

- Mosciki et al in 1994: Western blot → 89% with progressing bilateral HL had Anti-68kDa antibody → antibody (+): 75% response to steroid therapy, antibody (-): 18%

- Gottschlich et al. in 1995: 90/279 (32%) with bilateral progressive SNHL had anti-68 kDa, only 5% of control subjects were seropositive
Clinical presentation

- Rapidly progressive (over weeks to months), sometimes over a few days or week
- HL initially is unilateral → bilateral HL occurred after weeks to months
- Hearing: Asymmetric, progressive, fluctuation
- Most occur in low and mid-frequencies
- Tinnitus and aural fullness: 25-50%
- 50% of p’t have vestibular dysfunction
- Respond to steroid treatment
Classification

- **Primary**: organ specific, restricted to the ear
- **Secondary (29%)**: organ-nonspecific multisystemic

Table II. Autoimmune diseases affecting hearing.

- Relapsing polychondritis
- Systemic lupus erythematosus
- Disseminated vasculitis
- Rheumatoid arthritis
- Sjögren’s syndrome
- Systemic sclerosis
- Myasthenia gravis
- Hashimoto’s thyroiditis
- Goodpasture’s syndrome
- Vogt-Koyanagi-Harada syndrome
- Cogan’s syndrome
- Behçet’s disease
- Sarcoidosis
- Wegener’s granulomatosis
Cogan’s Syndrome

- **Typical**: Reversible interstitial keratitis
- **Atypical**: uveitis, iritis or conjunctivitis
- Vertigo, tinnitus, SNHL (mild to moderate)
- Syphilitic test: negative
- Commonly occurs in 20s or 30s
Vogt-Koyanagi-Harada syndrome

- Similar to Cogan’s disease
  - SNHL, vestibular signs (75%)
  - Bilateral granulomatous uveitis
- Auditory and ocular symptom occurred almost the same
- Autoimmunity to melanocytes \(\rightarrow\) alopecia and vitiligo, depigmentation of the hair and periorbital
- Aseptic meningitis
Wegener’s granulomatosis

- C-ANCA 90% specific
- Necrotizing granuloma and small to medium-size vasculitis
- Upper airway, eye and ear:
  - Nose: pain, nasal bleeding, crusting, *saddle-nose*
  - Ears (30 to 50%): middle ear disease, such as COM, conductive HL, serous OM, SNHL (10%)
  - Oral cavity: non-specific ulcerations
  - Eyes: pseudotumours, scleritis, conjunctivitis, uveitis, episcleritis
- Kidneys: glomerulonephritis (75%) → chronic renal failure
- Pulmonary nodules, cavitary lesions, and rarely bronchial stenosis
Rheumatoid Arthritis

- Small joints of hands and feet
- Vasculitis, muscle atrophy, subcutaneous nodules, splenomegaly
- 44% bilateral SNHL
Systemic Lupus Erythematosus

- Numerous systemic manifestations
- Mouth and nose ulcers
- Anti-nuclear, anti-dsDNA antibodies
- COM, SNHL (58%), dysequilibrium
Epidemiology

- Precise incidence can’t be determined
  - lack of a definitive diagnostic test

- AIED is a rare disorder → less than S.D (1/5,000~10,000 per year)

- In both sexes (F 63~65% > M) and can begin in children

- Usually 30 - 50 years

- Occasionally only one ear is affected initially → bilateral (79%)
Pathogenesis

- Vasculitis of vessels supplying the inner ear
- Autoantibodies directed against inner ear antigen
- Cross reacting theory
Pathogenesis (animal studies)

- Antigen $\rightarrow$ ICAM-1 on endothelium of **spiral modiolar vein** $\rightarrow$ lymphocytes migrates from the systemic circulation to inner ear $\rightarrow$ enter **the scala tympani**

Harris *et al.*
Harris and Sharp (Autoimmune response in the inner ear, 1987)

- Bovine temporal bone antigen, systemically immunize guinea pigs
  - Cause to HL
  - Western blot: specific antibody binding to a 68-kDa bovine inner ear antigen (35%)
  - The same antibody will also bind to the bovine heat shock protein-70 (HSP-70)
  - This antibody has been found in humans
Pathogenesis (animal studies)

- Zajic et al, Ptok et al, Nair et al and Disher et al (Antibodies to the inner ear cell),
- Chick and guinea pig inner ear extracts immunize mice
  - Induce HL
  - A monoclonal antibody binds to supporting cells of the organ of Corti: KHRI-3 (68-72 kDa)
  - Antibody-mediated pathology within the cochlea
Pathogenesis
(animal studies)

- **SLE mouse model:**
  - Elevations in auditory thresholds
  - Degeneration of the *stria vascularis*
  - Antibody deposition within the *stria capillaries* with absence of inflammatory response
  - Corticosteroid improved cochlear function
Pathogenesis (human temporal bone studies)

- Wegener’s granulomatosis, polyarteritis nodosa, Cogan’s syndrome, and SLE
  - fibrosis and osteoneogenesis within the scalae
  - changes more consistent with ischemia
    - cellular atrophy
Diagnostic method

- No golden standard criteria
- 1. History taking
  - Auditory or vestibular symptom
- 2. Physical exam: OME
- 3. Past history:
  - previous otologic surgery, ototoxic drug use, and concurrent URI, trauma
  - Past medical history: DM, autoimmune disorders, malignancies, neurologic condition (Multiple sclerosis)
Diagnosis method

4. Review of systems
   - ocular disease, nephritis, arthritis, sinusitis, and inflammatory bowel disease
5. Audiometry
6. Lab data
   - Routine serologic tests
     - CBC/DC, glucose, cholesterol/TG, ESR, CRP, RA, ANA, ANCA, anti-dsDNA anti-SSA/B, antiphospholipid/anticardiolipin antibodies
     - C3; C4 complement
     - FTA-ABS, MHA-TP (r/o otosyphilis), Lyme titers
7. Image: r/o retrocochlear lesion, acoustic tumors, and cerebrovascular accidents
8. **Western blot:**
   - A. Detection of anti 68-kDa antibody
   - B. Billings at al.: 70 kDa Heat Shock Protein (HSP-70), normal people: 5%
   - C. Valid of 68 kDa: (1999, Hirose K)
     - Sensitivity: 42%; specificity: 90% (false positive 10%)
     - High positive predictive value: 91%
     - Predicting response to steroid therapy
       - Anti-HSP(+): 75% response to steroid
       - Anti-HSP(-): 18% response to steroid
The best predictive value for steroid is the Western blot for Hsp 70.

### TABLE III.
Were Any Abnormal Tests Predictive of Steroid Response?

<table>
<thead>
<tr>
<th>Abnormal Result</th>
<th>Steroid Responsive</th>
<th>No Steroid Response</th>
<th>Normal Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western blot*</td>
<td>10/24 (43%)</td>
<td>1/10 (10%) (P&lt;.01)</td>
<td>23/34</td>
</tr>
<tr>
<td>ESR</td>
<td>2/22 (9%)</td>
<td>3/10 (30%)</td>
<td>27/32</td>
</tr>
<tr>
<td>CRP</td>
<td>3/21 (14%)</td>
<td>3/10 (30%)</td>
<td>25/31</td>
</tr>
<tr>
<td>Clq</td>
<td>3/20 (15%)</td>
<td>4/10 (40%)</td>
<td>23/30</td>
</tr>
</tbody>
</table>

*By Fisher’s exact test, there was evidence of difference between the steroid responsive and nonresponsive groups (P < 0.05).

Note: Values are no. (%).

<table>
<thead>
<tr>
<th>Steroid Response</th>
<th>Positive</th>
<th>Negative</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>10</td>
<td>1</td>
<td>91%</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
<td>9</td>
<td>(n = 34)</td>
</tr>
</tbody>
</table>

Sensitivity = 42%
Specificity = 90%
9. **Clinical:**

- Progressive SNHL, bilateral
- Symptom improvement after high dose steroid (1mg/kg/d 2-4 wks)
- fail to conventional medical treatment (low salt diet or diuretics)

10. Diagnostic biopsy of inner ear : not feasible, major obstacle
Differential diagnosis

- Sudden deafness
  - Sudden HL is always unilateral
  - Developed in 72 hours or less
- Meniere’s disease
  - Difficult to differentiate in the first months $\rightarrow$ 25-50% AIED were previously diagnosed MD
    - fluctuation SNHL
    - episodic vertigo
    - aural fullness
- Autoimmune etiology ?
  - 32% with anti-68kDa antibody
Differential diagnosis

- **Otosclerosis**: positive family history, excellent discrimination, flat audiometry curve, progression over a matter of years
- **Otosyphilis**
  - Sudden HL, progressive, episodic vertigo over months or years; serologic test (VDRL, RPR, FTA-ABS, MHA-TP)
- **Acoustic neuroma**
  - sudden or progressive unilateral SNHL
- Rare: meningitis, multiple sclerosis, or malignancy (eg, metastatic disease, lymphoma)
Treatment

- **Corticosteroid therapy** (Hughes, improved 40 %, stable 45%, decrease 15%)
  - Response
    - 60 mg -> 40 mg ➔ 30 mg ➔ 20 mg ➔ 15 mg ➔ 10 mg for 6th month
    - Maintenance dose of 10-20 mg/day may be indicated
  - Fail
    - Rapidly tapered off over **a week to 10 days**
    - Relapse on the taper: high dose prednisone (up to **2 mg/kg**)
    - Still relapse on the taper; add Methotrexate (MTX) or cyclophosphamide (Cytoxan)
Treatment

- **Methotrexate** (dihydrofolate reductase inhibitor)
  - Sismains et al in 1994 laryngoscope: 5 p’t → effective
  - Harris et al in 2004 JAMA: a randomized control trial: **No difference** after steroid between MTX and placebo groups
  - Side effect: Myelosuppression (leucopenia, thrombocytopenia and anemia), acute hepatotoxicity, urticaria
  - 7.5-15mg weekly with folic acid (FDA)

- **Cyclophosphamide**
  - Sismains et al: 1-2 mg/d, improved **70-80%**
  - Side effect: Myelosuppression (leucopenia, thrombocytopenia), hemorrhagic cystitis, bladder cancer, interstitial pulmonary fibrosis
Treatment

- **Etanercept** (an inhibitor of TNF receptor) → anti-inflammatory
  - 2005. Stanley Cohen: 25 mg SC twice weekly for 8 weeks, **no effective**

- **Intratympanic steroid**: **not** encouraging
  - Yang GS: et al in 2000: didn’t suppress inner ear HL

- **Plasmapheresis**, Luetie in 1997
  - Removal of antibodies, antigens and immune complexes
  - 6/12 patients; **50%** patients have improved over the average 6.7-year follow-up
  - The stronger the evidence for AIED, the more likely a favorable result
Conclusion

- The inner ear is not an “immunologically privileged” site
- The pathophysiology of AIED is still not well understood
- No uniform criteria for diagnosis
  - clinical presentation
  - response to the corticosteroids
- Treatment options are limited
  - corticosteroids being the only validated
- Recovery rate from 47-63% (partial and complete recovery)
Reference

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Thanks for your attention!!