Autoimmune Inner Ear Disease

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Outline

- History
- Definitions
- Proposed pathophysiology
- Treatment(s)
- Case Study
History

• 1979 – McCabe (1)
  • 18 pts w/ idiopathic rapidly progressive, B/L SNHL
  • Regained hearing after Tx w/ cyclophosphamide and dexamethasone
• 1990 – Harris & Sharp (2)
  • Circulating Ab against inner ear Ag detected by use of Western blot
• 1994 – Moscicki, Martin, Quintero, et al. (3)
  • Demonstrated circulating serum Ab reaction w/ 68-kD protein of bovine inner ear and renal extract in pts w/ idiopathic, progressive, B/L SNHL (IPBSNHL)
• 1995 – Billings, et al (4); Bloch, et al. (5)
  • Identified the 68-kD protein Ag as HSP 70
Definitions

• Autoimmune Inner Ear Disease (AIED)

  • Likely immune-mediated disorder
    • Unknown whether etiology is autoimmune – indirect evidence
    • Nomenclature
      • “Autoimmune” coined by McCabe → established in literature
      • Preferred: Immune Mediated Inner Ear Disease

• Classic definition
  • Rapidly progressive (over wks-months) bilateral SNHL (with or without vertigo) that responds to administration of immunosuppressive agents
AIED

• Primary AIED
  • Immune mediated idiopathic bilateral progressive SNHL (IBPSNHL) due to pathology restricted to ear

• Secondary AIED
  • Immune mediated IBPSNHL due to multisystemic, organ non-specific autoimmune disease that also involves inner ear
    • Cogan’s, Wegner’s, SLE, rheumatoid arthritis, systemic vasculitides, Scleroderma, Sjogren’s, ankylosing spondylitis, celiac disease, ulcerative colitis, relapsing polychondritis, sarcoidosis, Bechet’s disease
Clinical Description

- Idiopathic, progressive, bilateral SNHL (IPBSNHL)
  - Evidence of progression of SNHL over > 3 days to months
    - Primarily bilateral (synchronous or asynchronous)
    - No specific audiometric profile
    - May be fluctuating progressive
  - w/ or w/o vertigo, ataxia and imbalance
  - Responsive to immunosuppressant medications (50-80%)
Immune Function of Inner Ear

• Blood-labyrinthine barrier
  • Maintains homeostasis inner ear
    • Maintains electrochemical balance cochlear fluids
    • Limited immunosurveillance
  • Minimal lymphatic drainage
• Inner ear contains immunoglobulins (1/1000th of serum – IgG>IgM>IgA), interleukins, TNF, interferons & immunocompetent cells (ELS)
  • Can cross blood labyrinth barrier
  • Immune responsiveness
Endolymphatic Sac

• Contains resident lymphocytes
  • Responsible for immunoglobulin production

• Allows for systemic lymphocyte entry into inner ear
  • Enter through spiral modiolar vein and collecting venules after stimulation by intercellular adhesion molecule (ICAM)
    • SMV located adjacent to the scala tympani
  • Ag from inner ear $\rightarrow$ ELS (flow) $\rightarrow$ stimulates lymphocytes to produce Ab
A: Cross section of a vein (arrow) on the floor of scala tympani. Note that it has only a thin connective tissue covering.

B: Longitudinal section of a vein (arrows) on floor of scala tympani. The vessel appears completely exposed to the perilymphatic space.
Dissection view of scala tympani and modiolus in the basal turn showing the posterior spiral vein (black arrows). A vein (white arrow) on the side of the modiolus joins the posterior spiral vein. Compare this image with the modiolar cross sections seen in slide 14. This preparation received light decalcification but no bone was removed from the modiolar wall. ST, floor of scala tympani.

The Endolymphatic Duct and Sac


AJNR: 18, May 1997

Fig 4. Photomicrograph of endolymphatic sac, transverse section in region of external aperture of vestibular aqueduct (hematoxylin-eosin, magnification ×63). The petrous bone is on top and the left. Note the large number of longitudinally oriented, cuboidal epithelium-lined tubules cut in cross sections, containing endolymph of light and dark staining properties. Several arterioles (two marked with arrows) and venules (one marked with curved arrow) lie in the abundant loosely areolar stroma, which merges gradually and indistinctly with the dense fibrous overlying and underlying dura at approximately the position of the open arrows. Towards the distal end of the sac not shown on this section, the tubules coalesce and become wider and fewer (courtesy of House Ear Institute, Los Angeles, Calif).
Type I Hypersensitivity

- Immediate
- IgE mediated
- Mast cells
- Histamine
- Vasodilation
- ? Hydrops
- Meniere’s
- Inhalant allergy
Type II Hypersensitivity

- Antibody dependent
- Complement activation
- Anti-68kDa protein antibody
- SLE, Goodpasture’s
Type III Hypersensitivity

- Immune complex
  - Ag/Ab
- Ig deposition
  - In microcirculation → immune activation
- Tissue injury
- Wegener’s, ?Menieres
Type IV Hypersensitivity

- T-cell mediated
- Direct lysis
- Lymphokine production
- Lymphocyte transformation test (LTT)
- Cogan’s syndrome
Clinical Presentation

- Middle-aged women (65% female: 35% male)

- Progressive (bilateral) SNHL, > 3 days – months
  - Less than three days Sudden Idiopathic SNHL (unilateral)

- Dizziness (vertigo, imbalance, ataxia), aural fullness

- Bilateral 79%

- Systemic autoimmune disease in 29%
Clinical Diagnostic Criteria

• Audiometric

  • B/L SNHL > 30 dB at any frequency w/ progression in @ least one ear
    • Progression: defined as a threshold shift > 15 dB at any frequency - OR - 10 dB at 2 or more consecutive frequencies - OR - a significant change in discrimination score (> 15%)

  • Excludes
    • Sudden SNHL
      • Occurring < 72 hours
Diagnosis

- Clinical
  - Response to PO steroids

- Lymphocyte Transformation Test (LTT)
  - 93% specific, 50-80% sensitive

- Western blot for anti-68kDa protein (hsp70)
  - 95% specific
  - Low sensitivity
  - Predictor of steroid response
Diagnosis

- ESR
- CRP
- C1q binding assay
- Anti-cardiolipin Ab
- ANCA
- ANA
- FTA-ABS
- Lyme titers

- CBC
- Chemistries
- Thyroid function
- RF
- Anti-SSA, SSB
- Imaging
  - MRI IACs w/ w/o contrast
Polyarteritis Nodosa

- Vasculitis of small and medium-sized arteries
  - Vasculitis w/ ischemia, osteoneogenesis and fibrosis

- Renal and visceral targets
  - Risk for CAD and Stroke

- Hearing loss rare
Cogan’s Syndrome

- Interstitial keratitis
  - Lacrimation, photophobia, pain
- Vestibulocochlear symptoms
  - Intermittent vertigo, tinnitus, SNHL
- Positive LTT to corneal Ag and inner ear Ag
Vogt-Koyanagi-Harada (VKH) Syndrome

- SNHL, vestibular signs, uveitis
- Periorbital hair loss, depigmentation
- Aseptic meningitis
- ?autoimmunity to melanocytes
Wegener’s Granulomatosis

- Necrotizing granuloma(s) w/ vasculitis in one or more organ system
  - Respiratory tract & kidneys
- Serous OM
- cANCA 90% specific
- Responsive to steroids
Behçet’s Disease
Relapsing Polychondritis

- Recurrent inflammation of cartilages of ear, nose, trachea, larynx
- Autoantibodies to type II & IX cartilage
- Rx: NSAIDs, steroids, dapsone
Systemic Lupus Erythematosus

- Anti-nuclear, anti-DNA antibodies
- Numerous systemic manifestations
- COM w/ vasculitis, SNHL, dysequilibrium
Rheumatoid Arthritis

- Small joints of hands and feet
- Vasculitis, muscle atrophy, subcutaneous nodules, splenomegaly
- IgM 19S and 7S, IgG 7S 75%
- 44% bilateral SNHL
Meniere’s Disease

- Fluctuating SNHL, episodic vertigo, aural fullness
- ? Autoimmune etiology
  - 97% with CICs (Derebery)
  - Response to immunotherapy
  - 32% with anti-68kDa antibody
Treatment AIED

• Steroids
  • Optimal dose?
    • Prednisone 60 mg PO q day 3-4 wks then taper slowly ~20 mg q other day 3-6 mo’s
  • Optimal delivery mechanism?
    • PO v Intratympanic

• Cyclophosphamide

• Plasmapheresis

• Methotrexate
  • Dihydrofolate reductase inhibitor
## Complications of therapy

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Cyclophosphamide</th>
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</thead>
<tbody>
<tr>
<td>Sodium retention</td>
<td>Nausea-vomiting</td>
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<tr>
<td>Potassium loss</td>
<td>Alopecia, skin rash</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hemorrhagic cystitis</td>
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<tr>
<td>Muscle weakness</td>
<td>Hemorrhagic myocarditis</td>
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<tr>
<td>Myopathy</td>
<td>Carcinogenesis (urinary bladder, myeloproliferative malignancies)</td>
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<tr>
<td>Osteoporosis</td>
<td>Sterility</td>
</tr>
<tr>
<td>Aseptic necrosis of femoral and humeral heads</td>
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<tr>
<td>Peptic ulcer perforation, hemorrhage</td>
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<tr>
<td>Glaucoma</td>
<td></td>
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<tr>
<td>Increased intraocular pressure</td>
<td></td>
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<tr>
<td>Cataracts</td>
<td></td>
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<tr>
<td>Increased intracranial pressure</td>
<td></td>
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<tr>
<td>Manifestations of latent diabetes mellitus</td>
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<tr>
<td>Cushingoid state</td>
<td></td>
</tr>
<tr>
<td>Pituitary, adrenocortical insufficiency</td>
<td></td>
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<tr>
<td>Nervousness</td>
<td></td>
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<tr>
<td>Insomnia</td>
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Medical Malpractice and Corticosteroid Use

John J. Nash, MD\textsuperscript{1,2}, Amanda G. Nash, JD\textsuperscript{3}, Matthew E. Leach, \textsuperscript{1} and David M. Poetker, MD\textsuperscript{1,2}

- Malpractice cases involving Otolaryngologists

Table 3. Cases Involving an Otolaryngologist

<table>
<thead>
<tr>
<th>Allegation</th>
<th>Reason for Steroids</th>
<th>Complication</th>
<th>Verdict</th>
<th>Award (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negligent use</td>
<td>Thyroiditis</td>
<td>Depression, anxiety</td>
<td>Defendant</td>
<td>0</td>
</tr>
<tr>
<td>Negligent use</td>
<td>Hearing loss</td>
<td>AVN</td>
<td>Defendant</td>
<td>0</td>
</tr>
<tr>
<td>Wrongful death, FTD</td>
<td>Allergic cough</td>
<td>Pulmonary tuberculosis, pulmonary hemorrhage</td>
<td>Plaintiff</td>
<td>2,000,000</td>
</tr>
</tbody>
</table>

Abbreviations: AVN, avascular necrosis; FTD, failure to diagnosis.

- Conclusions
  - Frequently used for treatment of otolaryngologic conditions
  - “Physicians should obtain informed consent prior to initiating of steroid therapy and realize malpractice litigation can result in large judgments against defendants.”
Case Study

• 66 year old male pt presented w/ bilateral Right > Left sided SNHL.

• AD – Severe HL present since 2 yrs prior to initial evaluation
  • S/P six AD trans-tympanic gentamicin perfusions for AD MD (last one performed 2 years prior to initial evaluation)
  • Continues w/ AD aural fullness and tinnitus
  • Vertigo controlled 2 yrs until prior to evaluation
    • 1 episode vertigo of 30 min – 1 hr duration followed by improvement in AS hearing loss following episode

• AS – slowly progressive non-fluctuating until 2 months prior to evaluation when pt c/o onset of left sided aural fullness and hearing loss
  • AS HL subjectively improved following last episode of vertigo
History

• PMH
  • OSAS, osteoarthritis, Gout, Type II Diabetes Mellitus, HTN, renal calculi, CAD (s/p CABG), Hx Pneumonia

• PSH
  • Knee and shoulder arthroscopy, TKR, CABG, PTCA w/ stent,
    • Ear: AD – IT dexamethsone, ELS/D w/ shunt, IT Gentamicin (x 6)
Medications

- Astelline, Lipitor, ASA, potassium chloride, ibuprofen, metformin, maxzide, elavil, diltiazem, enalapril, pepcid, flomax, allopurinol, metoprolol
Physical Exam

• Unremarkable except

  • Tuning fork testing – 512 Hz
    • AD: not detected
    • AS: AC > BC
    • Webber lateralized Left
Case Study, continued

- CBC, ESR, CRP normal

- GFR 55 (L), TSH normal, Free T4 low, FTA-ABS negative

- MRI IACs w/ w/o contrast – “unremarkable”
1: Tactile response

TYmps: normal bilaterally.

Speech Reception Threshold and Word Recognition: live voice

Right Ear: Speech Awareness 85 dB HL (masked)
Left Ear: 10 dB HL with 86 % word recognition at 50 dB HL with no dB masking
Plan

- Continue low salt diet, Maxzide, allergy testing w/ initiation of immunotherapy if indicated
  - Discussed PO steroid v AS IT dexamethasone v observation for 4 wks
    - Pt chose to observe as he felt he was improved (hearing and balance) and did not wish to take PO steroids due to Type II DM

- F/u w/ PCP/IM to initiate thyroid medication
Follow UP

• No major episodes of spinning vertigo
  • several brief episodes of seconds duration

• Significantly decreased AS hearing sensitivity
  • Denies AS tinnitus

• C/o fluctuating AS aural fullness
  • On exam pt w/ persistent AS aural fullness in association with worsening hearing loss
Speech Reception Threshold: Right at DNT dB HL; Left at 50 dB HL (live voice)
Word Recognition Testing: Right: DNT Left 84 % at 80 dB HL (0 dB masking) (live voice)

Right ear: profound sensorineural hearing loss
Left ear: moderate to profound sensorineural hearing loss
Treatment

• Discussed PO steroid (High-Dose Prednisone) v AS intratympanic dexamethsone perfusion

  • AS Dexamethasone Perfusion (10 mg/ml)
    • Single trans-tympanic dexamethasone perfusion
Follow up

• s/p 1 week post AS IT Dexamethasone perfusion
  • Pt w/ 1 episode of severe room spinning vertigo (1 hr duration) in association w/ AS aural fullness and decreased hearing 3 days following IT dexamethasone
  • On follow up pt with improved hearing (not back to baseline) but w/ improved balance
*=June 15, 2012
C=2-29-12

Left: mild to profound SNHL, considerably better than last week, but LF did not completely return.
Right: profound SNHL documented in Feb 2012.

Speech Reception Threshold and Word Recognition: live voice

Right Ear: DNT
Left Ear: 15 dB HL with 80 % word recognition at 55 dB HL with -- dB masking
Treatment

• Rheumatology consultation – Immune mediated inner ear disease
  • Steroid maintenance after series of IT dexamethasone
    • Could not tolerate 20 mg q other day – had to taper down to 5 mg daily

• Series of 4 IT dexamethasone perfusions
  • Hearing returned to “normal” and stable w/ resolution of symptoms x 5 months duration
6 mo Follow up

- Pt w/ fluctuating AS hearing loss, aural fullness and 2-3 episodes of vertigo of minutes duration over last 3 wks prior to evaluation

- PO steroid Prednisone begun 2 wks prior to evaluation in office
  - 30 mg PO q day x 12 days
    - Pt c/o worsening blood sugars, insomnia, GI discomfort

- Hearing returned to normal and vertigo resolved x 2 wks until day before evaluation (after completing PO steroid) when hearing decreased again AS w/ increased AS aural fullness
Speech Reception Threshold: (live voice)
Right: DNT dB HL
Left: 50 dB HL

Word Recognition Testing: (live voice)
Right: DNT % presented at -- dB HL, (-- dB masking)
Left: 88 % presented at 80 dB HL (-- dB masking)

Pure tones:
RE: DNT
LE: Moderate to profound sensorineural hearing loss
Treatment

• Discussed PO steroid maintenance v IT steroid
  • Pt wished to avoid PO steroids
  • Series of 4 IT Dexamethasone perfusions
• Resolution of vertigo w/ improvement in hearing loss x 6 months
Speech Reception Threshold: Right DNT; Left at 30 dB HL (live voice)
Word Recognition Testing: Right: DNT; Left 80 % at 60 dB HL (no dB masking) (live voice)

Right ear: DNT
Left ear: mild to profound hearing loss; improved in low and mid frequencies since 12/21/2012
Patient test reliability was excellent.
Conclusion

• AIED/Immune mediated inner ear disease
  • Elusive etiology
    • Makes diagnosis and treatment difficult

• Potentially treatable cause of bilateral progressive SNHL

• Long term needs
  • Less toxic therapy

  • Better “diagnostic” test(s)
References

References