Autoimmune Inner Ear Disease (AIED)

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Definition:

- (RPSNHL) (rapidly progressive SNHL) –
  - 30 dB or greater SNHL over at least three contiguous audiometric frequencies occurring over weeks to months

- SSNHL (Sudden SNHL) –
  - 30 dB or greater SNHL over at least three contiguous audiometric frequencies occurring in ≤3 days
Theories

- Viral
- Autoimmune (autoimmune inner ear disease – AIED)
- Vascular
- Intracochlear membrane breaks
Introduction - AIED

- Relatively new etiologic mechanism for sudden or rapidly progressive hearing loss
- Inner ear proteins recognized as foreign or non-self
  - Primary process
  - Secondary to trauma or inflammation
Introduction - AIED

- Some clinicians doubt the existence of the disease
  - Inner ear antigens not yet known
  - Inability to evaluate histopathology
Introduction - AIED

- Important for physicians to understand the concept of the disease
- Treatable cause of SNHL
- Treatment must be started early in the disease course
Introduction - AIED

- Devastating to patients
- Frustrating for physicians
Take Home Message

- **AIED**
  - Rapidly progressive (weeks to months) bilateral SNHL
  - Responds to immunosuppression
  - Treat with steroids first
  - +/- cytotoxic drugs
Introduction - AIED

● 1979 – McCabe first described AIED
  ● Series of 18 patients
    ● Bilateral, rapidly progressive SNHL
    ● 100% had a + Lymphocyte transformation test (LTT) compared to 0% in controls
    ● Hearing improved with steroids
    ● One temporal bone showed vasculitis
Inner Ear Immunology

- Inner ear is not immune privileged
- Endolymphatic sac contains immunocompetent cells (Takahashi, 1988)
  - Site of antigen processing in the inner ear
  - Protects other inner ear sites from foreign or infectious agents
  - Protects from immunologic damage
Inner Ear Immunology

- Cochlea is devoid of immune cells
- Antigens or protein injected into the scala tympanic will reach the endolymphatic sac (Yeo, 1995)
Inner Ear Immunology

- Evidence of inner ear autoimmunity
- Loss of hearing in animals immunized with inner ear proteins (Orozco et al., 1990)
Evidence lacking to support autoimmunity in the inner ear

- No antigen found as a single target of autoimmunity

- Candidate antigens proposed
  - 68 kDa protein linked to hsp 70
  - Type II collagen
  - Many more
Histopathology
- Postmortem examination has shown osteoneogenesis
- Unable to exam T-bone during disease activity

Response to immunosuppression
- Animals pretreated with cyclophosphamide prior to viral insult have reduced hearing loss (Darmstadt et al.)
- Steroids and cytotoxic agents are not specific to immunity
History

- Time course
- Associated symptoms
  - Vertigo/dizziness
  - Aural fullness
  - Tinnitus
- Ototoxic drug use
- Symptoms of URTIs
- H/O head trauma, straining, sneezing, nose blowing, intense noise exposure
- H/O flying or SCUBA diving
History

- PMH:
  - Autoimmune disorders
  - Vascular disease
  - Malignancies
  - Neurologic conditions
  - Hypercoagulable states
    - Sickle cell disease (African Americans)

- PSH: stapedectomy or other otologic surgeries
Physical Exam

- Complete H&N exam
  - Ears: r/o effusions, cholesteatoma, cerumen impaction
  - Weber/Rinne
  - Neurologic exam – cerebellar findings
    - Tandem gait
    - Romberg
    - Nose to finger, heel to shin
- Vestibular – Dix-Hallpike test
Diagnosis

- AIED – classified as a cause of SSNHL
  - More commonly RPSNHL
  - Bilateral and asymmetric
  - 50% with vestibular symptoms
    - Ataxia or light-headedness
    - Episodes are multiple times daily
    - Vestibular testing reveals bilateral reduced responses
  - Slight predominance in middle-aged females
  - < 30% have systemic autoimmune disease
Diagnostic Testing

- Audiogram – diagnostic and prognostic
  - Pure tone
  - Speech discrimination
  - Tympanometry
  - Stapedial reflex
Diagnostic Testing

- Laboratory testing
  - CBC
  - ESR, CRP
  - Chemistry
  - Cholesterol/triglycerides
  - T3/T4, TSH
  - RPR, VDRL
  - HIV
  - Lyme titer
  - Antigen-specific cellular immune tests
    - Lymphocyte transformation test (LTT)
    - Western blot
Diagnostic Testing

- MRI:
  - Rule out cerebellopontine angle tumors
  - Multiple sclerosis
  - Ischemic changes
- 10%-19% of patients with acoustic tumors present with SHL
- 23% may recover hearing
- 1% of patients with asymmetric SNHL have acoustic tumors
Diagnosis

- No test to definitively diagnose AIED
  - Dx currently based on
    - sudden or RPSNHL,
    - Responsiveness to immunosuppressive therapy,
    - +/- positive LTT or Western blot
Diagnosis

Hughes (1996) –

- Lymphocyte transformation test
  - Sensitivity – 50-80%
  - Specificity – 93%
  - Positive predictive value 56-73%

- Western blot
  - Sensitivity – 88%
  - Specificity – 80%
  - Positive predictive value – 92%
Diagnosis

- Currently antigen-specific cellular immune tests are not used routinely by most clinicians
  - Availability
  - Does not change management
    - Low sensitivity
  - Experimental
AIED

- Ideal test for AIED
  - Marker specific for AIED

- 1990 – Harris and Colleagues
  - Used Western blot to discover anti 68kDa autoantibody in sera of patients with Idiopathic sudden or RPSNHL

- 22%-89% will have +test
Moscicki (1990)

- Run test during disease activity
- 94% specificity
  - Correlating results with responsiveness to therapy and disease activity
Further studies

- Billings and Harris
  - Linkage of 68KD protein to heat shock protein 70 (hsp 70)

Theories

- 1) Cross reactivity
- 2) Over expression leads to autoimmunity
  - Gong and Yan (2002) – increase expression of hsp 70 in guinea pigs immunized with CIEAgs
Trune et al. (1998)
- Could not induce hearing loss with hsp 70 in guinea pigs

Harris
- Could not induce hearing loss in immunized mice with hsp 70
Multiple other candidate antigens have been proposed:
- Type II Collagen (Yoo et al., 1982)
- Beta tubulin (Connolly et al., 1997)
- 30 kDa protein
- c Raf
Autoimmune SNHL

- Cogan’s syndrome
- Wegener’s granulomatosis
- Polyarteritis nodosa
- Temporal arteritis
- Buerger’s disease (Thromboangitis Obliterans)
- Systemic Lupus Erythromatosis
Autoimmune SHL

- **Cogan’s syndrome**
  - First described by Cogan in 1940
  - Autoimmune disease of the cornea and inner ear
  - Age of onset 22-29 years
  - Presentation – interstitial keratitis and Meniere’s like episodes of vertigo with BRPSNHL
  - Associated systemic diseases
    - Takayasu’s like or medium-sized vessel vasculitis
    - Aortitis – 10%
Cogans’s Syndrome
Autoimmune SHL

- **Cogan’s Syndrome**
  - Hearing fluctuates with disease exacerbations and remissions
  - Majority develop bilateral deafness (67%)

- Etiology is unknown
  - ? Microbial etiology
    - *Borrelia burgdorferi*
    - *Chlamydia species*
Autoimmune SHL

♦ Cogan’s Syndrome

♦ Diagnosis –
  ♦ Requires both eye and inner ear manifestations of inflammation
  ♦ CBC, ESR, RPR, FTAbs
  ♦ MRI/CT

♦ Therapy – Same as for AIED
Treatment

- Controversial
- Varied
- Lack of double-blind, prospective clinical trials
- Consensus – steroids are effective and should be used
Treatment

- Prednisone 1mg/Kg/day for 4 weeks
- Slow taper
- Relapse during taper – restart
  - (?higher dose)
- Slow taper
- If relapse during taper – Cytotoxic agent
  - Methotrexate (7.5-15mg weekly + folic acid)
  - Cyclophosphamide (100mg po bid)
- Monitor electrolytes, LFTs, blood counts, U/A
- Rheumatology consultation
Treatment

McCabe favors starting with cyclophosphamide and prednisone from the start
Treatment

1996 - Review by Hughes

- Recommendations for treatment
  - Low salt (2g/day diet) and Maxide once daily
  - Prednisone 1mg/kg/day
  - Acyclovir 1-2 g orally daily in five divided doses for 10 days
Treatment Data

- Sismanis 1997 – MTX
  - 69.6% with hearing improvement
  - 80% with vestibular improvement

- Matteson (2001) – prednisone
  - 72% w/ hearing improvement

- Moscicki (1994) – prednisone
  - 75% w/ hearing improvement w/ + Western blot
  - 18% w/ - Western blot
Treatment Data

- Harris (2003)
  - 57% improved on prednisone
  - Found that MTX did not have any affect on maintenance of hearing improvement compared to placebo

- Lasak (2001)
  - Prednisone had more effect on PTA
    - (14.8 vs. 4.5 dB)
  - Cytotoxic drugs had more effect on speech discrimination
    - (26.2 vs. 6.9%)
Treatment

- Steroids
  - 1980 – Wilson and colleagues
    - Double-blind studies with oral steroids in patients with SSNHL
    - Decadron given over 10-12 days
    - Patients stratified based on audiogram
    - Results: steroids work in patients with hearing loss between 40 and 90 db
    - No effect for patients with >90 db
    - Midfrequency loss – patients excluded from study
  - 1984 - Findings confirmed by Moskowitz
Fig 2.—Categories of sudden hearing loss as determined by spontaneous recovery rate and response to steroid therapy.
Plasmapheresis

- Proposed by Luetje (1989)
- 1997 – Luetje reported on 21 patients
  - Several had remarkable improvements in hearing
- If available, reserved by most for immunosuppressive treatment failures
Some patients will progress to bilateral profound deafness
- Remember cochlear implantation
- Excellent candidates
Prognosis

- Natural course of AIED is not known
- 47%-63% w/ SSNHL spontaneously resolve
  - Combined patients with all audiogram types
- Four prognostic variables
  - Time since onset
  - Audiogram type
  - Vertigo
  - age
Prognosis

1984 – Byl

- 8 year prospective study of 225 patients with RPSNHL or SSNHL
- Looked at factors for prognosis
  - Age
  - Vertigo
  - Tinnitus
  - Audiogram pattern
  - Time elapsed on presentation
  - ESR level
Prognosis

- Age - <15 and >65 years had worse prognosis
Prognosis

- **Vertigo** – 29% recovery if affected
  - 55% if not affected

Fig. 2. Recovery related to erythrocyte sedimentation rate (ESR) and vertigo.
Prognosis

Audiogram type

SRT, 30 dB Discrim 52%
Best

SRT, 85 dB Discrim 24%
Worst
Prognosis

- 56% recovery presenting within 7 days onset
- 27% presenting 30 days or later
Conclusion

- Devastating to patients
- Frustrating for physicians to dx and tx
- Thorough H&P
- Rule out treatable cause
- Directed labs, Audiogram MRI
- Discuss risks, benefits, and alternatives of treatment with the patient
- Treat the disorder aggressively
- Rehabilitate those whose hearing does not improve
- Follow patients for development of associated diseases and for contralateral ear disease
Future

- Improved understanding of immunologic events in the inner ear
- Balance of Th1 and Th2 lymphocytes
  - Th2 – maintenance of “tolerance”
  - Understanding the role of Th2 gene products
- May lead to new immunotherapeutic strategies