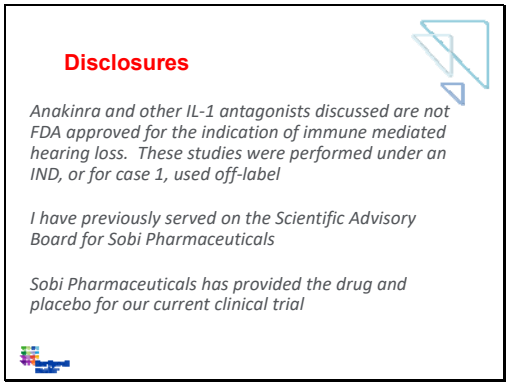
Slide 1

Slide 2



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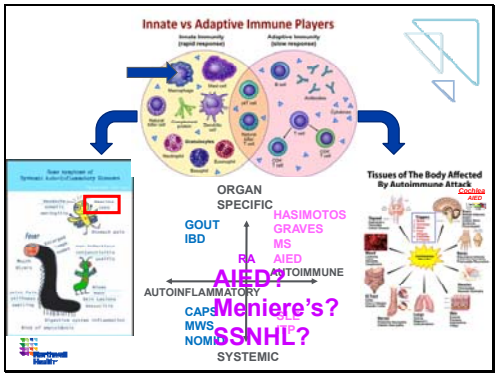


Slide 4

Case: 13 year old boy with fluctuating hearing loss with tinnitus

Chief Complaint:

- fluctuating, but progressively worsening hearing loss

History of Present Illness:

symptoms initially began at the end of an asthma exacerbation when patient was found to be "mumbling" at age 10

- denies vertigo, aural fullness, head trauma, headaches or history of otitis
- Dx "malingering" by other ENT

Slide 5

Clinical Profile

Case History, Exam, Labs, Imaging… all unremarkable

Bloodwork is not helpful in determining treatment or making a diagnosis

Frequent antibiotics for sinus infections

Mold sensitivity by history, positive skin testing

Mother is IgA deficient/ Hashimotos disease

Father with JRA

tympanic membranes, auricles and EAC's normal appearing bilaterally

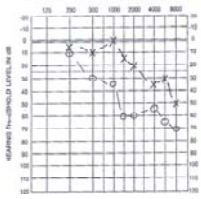
cranial nerve exam, cerebellar exam and gait normal

ANCA panel, IgG quantification, anticardiolipin, Sjogren, anti-smooth muscle, anti-mitochondrial, lyme EIA/immunoblot, RPR, ACE, anti-thyrogluobulin and anti-HSP-70 all NORMAL, Muckle Wells testing negative

Imaging: CT Temporal bones: *normal* anatomy, no LVA; MRI: *normal*

Slide 6

Clinical Audiology and Treatment History course over several years



Placed on prednisone – unable to taper

Flux correlates with steroid dose

No benefit w/ dyazide

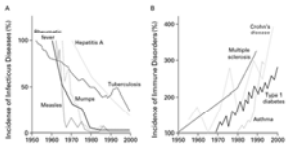
Add methotrexate – unable to taper

MT for IT steroids

TM perf develops

Slide 7

Autoimmune & Allergic Disorders are increasing in incidence



Bach, NEJM, 2002

Affects 14-23 million people, up to 8% of the population
More than 80 distinct diseases

Autoimmune Disease Research Plan 2005, NIAID

Slide 8

Reversible Sensorineural Hearing Loss

28 million Americans have hearing loss
Progressive, reversible, sensorineural hearing loss as a result of a primary inflammatory or autoimmune condition of the inner ear or a systemic immune condition.
Conditions include Sudden Sensorineural HL (SSNHL), and Meniere's Disease, and Autoimmune Inner Ear Disease (AIED)
Characterized by episodic and sudden loss of hearing w/ or w/o tinnitus and possibly dizziness.
Diagnosis: DIFFICULT– NO SPECIFIC BIOMARKER – SPECTRUM
AIED is an *unclassified* orphan disease, affecting < 1% of Americans of the 28 million with hearing loss
Meniere's may also fit orphan disease definition.

Slide 9

Immune Mediated Hearing Losses

SSNHL: Most common: Unilateral acute loss of hearing in >3 days & >30dB drop at >3 contig frequencies

Meniere's Disease: Concurrent unilateral vertigo, loss of hearing, tinnitus & aural fullness (b/l in up to 23% LT)

AIED: Fluctuating SNHL, in absence of concurrent vertigo
Both ears should be afflicted but usually do not simultaneously fluctuate

? Noise Induced hearing loss/acoustic trauma

Slide 10

Prevalence of SSNHL, MD vs. AIED stats

- SSNHL Prevalence: 1-6/5,000/year Pop 300,000,000
- Or 1/60,000-1/10,000
- Or 5,000-30,000 per year
- NIDCD Website

** May be underreported as many do not seek treatment

Meniere's Disease : 615,000 individuals in the US Prevalence: 45,000 new cases per year NIDCD Website

- AIED – statistics: <1% of SNHL (Bovo et al, 2006)
- AIED <<SSNHL rate of 5-20/100,000 per year (George and Pradhan 2009)
- P=5/100,000/year x 3 years=15/100,000. US pop=300,000,000, therefore prevalence = 45,000 persons with AIED, or 15k/year, max (Vambutas & Pathak 2016)

Prevalence: Proportion of population affected during a given time

Slide 11

What can we expect in response to giving prednisone?

Slide 12

Corticosteroid response rates for SSNHL

65% OF SSNHL SPONTANEOUSLY RECOVER WITHOUT TREATMENT, TYPICALLY WITHIN 14 DAYS *Mattox 1977, Annals ORL*

61% RR COMPARED TO 32% OF UNTREATED *Wilson, Arch Otolaryngol 1980*

IN SEVERE-PROFOUND SSNHL, SIGNIFICANT IMPROVEMENT SEEN WITH CORTICOSTEORID USE (10 YR RR) *Chen Halpin Rauch, Otol Neurotol 2003*

IN PROSPECTIVE CT OF 250 PTS, INTRATYMPANIC THERAPY NOT INFERIOR TO ORAL CORTICOSTEROIDS, *Rauch et al, JAMA 2011*

COMBINATION OF HIGH DOSE CORTICOSTEROIDS WITH INTRATYMPANIC THERAPY IN A SERIES OF 51 PTS IN 3 ARMS *Battaglia , Otol Neurotol, 2008*

Slide 13

Corticosteroid response rates for Meniere's Disease

OTO-104 reduced number of vertigo days, daily vertigo count and severity, phase II Results: Lambert et al, Otol Neurotol 2016

AVERTS-1 phase III trial of OTIVIDEX for Meniere's 8/30/17: Missed primary endpoint and all key vertigo 2nd endpoints Globe Newswire

Vertigo improved with ITD but not hearing (series 51pts) Leng, Acta Otolar 2017

In a series of 34 patients with MD, 48% experienced avg PTA reduction 8.6dB (p=0.004) Hereiaz Otol Neurotol 2010 ***Similar to AIED response 4.1dB Niparko 2005*

In a series of 50 patients with MD that received IT steroids, 40% experienced hearing improvement (avg 14.2 dB) Hillman, Arriaga, Chen Laryngoscope 2003

Slide 14

Natural History of AIED Patients

*SNHL of greater than 30dB at 1+ frequencies in *both* ears with active deterioration in at least one ear 15 dB developing in >3 days but <90 days

STEROID RESPONDERS

Of the 60% that initially respond, only 14% remain responsive after 34 mos

Broughton & Meyerhoff

STEROID RESISTANT:

CONTINUED PREDNISONE THERAPY: Risks: HTN, DM, Osteoporosis, AVN, Psychosis, etc

Methotrexate Ineffectual (Harris et al, 2003)

TNF ANTAGONISTS Ineffectual/Limited by systemic Administration route (Cohen et al, Matteson et al) But good for control of Steroid dependent patients (VanWijk et al, Derebery et al)

Rehabilitative Strategies: Hearing Aids & Cochlear Implants

No effective way to identify and treat patients who are steroid resistant to restore natural hearing

Slide 15

Antigen specificity?

Or the muddy story of HSP70….

There is no single antibody associated with AIED
Is this one disease or many- the common link is *MISSING*
30% have concurrent systemic AI disease
20% will later manifest systemic autoimmune disease (Hughes, 1983)

Serum target antibody in patients with idiopathic progressive SNHL is HSP70 *(Bloch et al 1995)*
HSPs ubiquitous proteins produced in response to various types of cellular stress – therefore NOT a pathogenic Ab
Marker of steroid-sensitive AIED and Meniere's Disease (59% b/l and 33% uni (Rauch et al 1995))

Slide 16

What's the difference between SSNHL, Meniere's & AIED?

The only difference is the groundhog is on a more regular schedule than AIED or MD patients, and groundhogs don't get SSNHL

Slide 17

The endolymphatic sac is the antigen processing site of the inner ear

The ES receives antigens and waste material via the endolymphatic duct

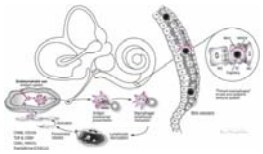
Resident macrophages/monocytes migrate into the sac lumen.

After phagocytosis, cells migrate back into the perisaccular tissue for antigen presentation and immune processing.

MHC II TLR4 – restricted (+IFNγ), bind to endocytosed, and degraded peptides within the cytoplasm and transport the peptides to the cell membrane for presentation to CD4+ T cells.

The lymphocytes recirculate into the bloodstream to "prime" the inner ear cells.

The chemokine fractalkine assists in attracting macrophages to the ES



Nordstrom et al, Frontiers Immunology 2018

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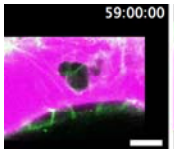
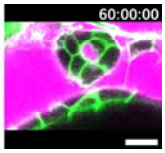
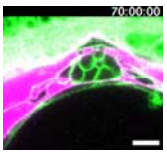






transcription factor lmx1bb mutant
Swinburne et al, eLife 2018

Lmx1bb mutants have reduced glutamatergic neurons
Hilinski et al, Neural Dev 2016

TNF & IL-1 inhibits astrocyte glutamate uptake
Hu et al, Neuroimmunomod, 2000

Slide 19

AIED & animal models? Witebsky's postulates ? fulfilled

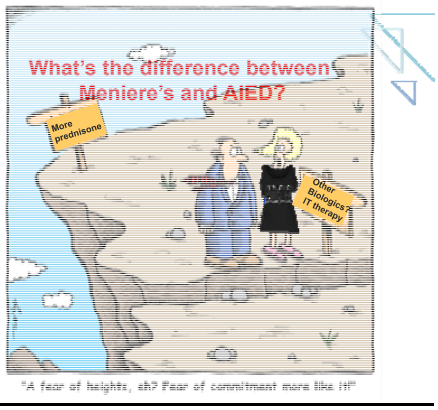
KLH model (guinea pig) *Harris, 1984*
Pseudo-autoimmune attack by intracochlear inoculation of KLH in primed animals
MRL/lpr mice – have hearing loss but do not recapitulate human disease
Cochlin vaccinated murine model: CD4 cell transfer results in disease, Th1-like (Solares)
Human study demonstrating cochlin specific T cells in humans (Baek)

Direct evidence from transf of pathogenic antibody or pathogenic T cells;

Indirect evidence based on reproduction of the autoimmune disease in experimental animals;

and circumstantial evidence from clinical clues.

Slide 20



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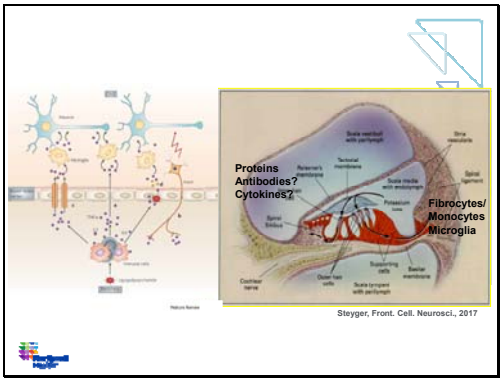

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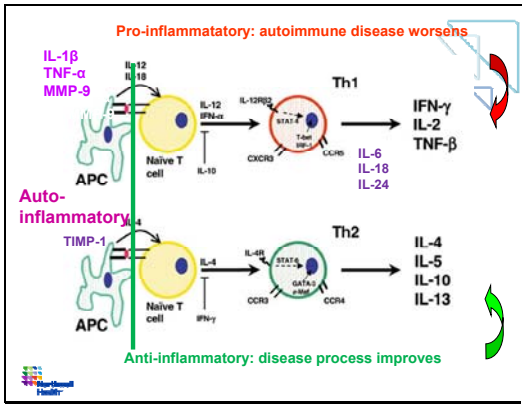


Slide 23

TNFα & IL-1β expression in inflammatory states in the inner ear

TNFα & IL-1β both expressed by infiltrating cells after KLH injection
IL-1β expressed during immune response and w/ surgical trauma
TNFα expressed in response to antigen (KLH) w/o trauma & Etanercept able to ameliorate TNFα (Satoh et al 2002) *the basis for TNF antagonist clinical trials*

Upregulation of IL-1β by fibrocytes: priming of inner ear via TLR4 (Hashimoto et al)

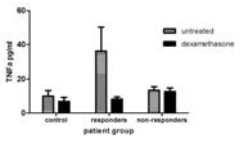
In SSNHL, greater # peripheral blood monocytes (26 v. 14), TNF-a 15.7 v. 12.4 in SSNHL v. controls (Yoon et al J Laryngol Otol 2019)

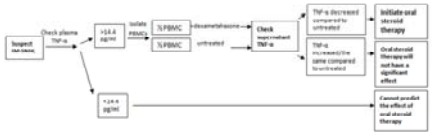
In acoustic trauma: ingress of macrophages to cochlea (Hirose et al 2005)
In acoustic trauma: upregulation of IL-1β, greater than TNF-α & constant low level IL-1RA independent of trauma (Fujioka et al 2006)

High basal levels of IL-1 in 20% of unilateral MD and 30% of bilateral MD; high levels of IL-1 & TNF in 36% of unilateral MD and 54% bilateral MD (Frejo Scientific Reports 2018)

Slide 24

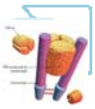
TNF LEVELS CAN PREDICT STEROID RESPONSE
Archives of Otolaryngology, Svrakic et al., Nov. 2012





Slide 25

TNF and hearing restoration



Systemic etanercept not better than placebo for 8 week study period n=20; 3 drop outs. *Cohen Otol Neurotol 2005*

Local perfusion of infliximab results in ability to taper CS in SD AIED patients (4/5) and hearing improvement in ¾ w/ relapse *Van Wijk Audiol Neurotol 2006*

10 steroid dependent patients treated with golimumab: 7 patients could completely be tapered off steroids and 3/7 experienced stability of hearing *Derebery Otol Neurotol 2014*

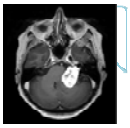
Slide 26

Acoustic Trauma: A common mechanism?

- Pro-inflammatory cytokines produced following noise exposure: IL-1β & TNFα
  - Fujioka et al, J Neurosci Res, 2006
- IT methylprednisolone reduces impact of intensive noise trauma on hearing (Zhou et al 2009)
- Treatment of Greek army soldiers with steroids & piracetam following acoustic trauma. 69% had some recovery if w/in 1st hour whereas if tx >24 hrs, 13% recovery. Psillas et al, 2008

Slide 27

TNF and Vestibular Schwannoma



Secreted factors from VS lead to cochlear damage

TNF-a was identified as the otoxic molecule in VS

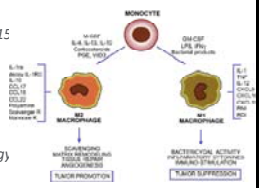
Ab mediated neutralization of TNF partially prevented hair cell loss

Dilwali et al Scientific Reports 2015

M2 macrophages seen in VS, and higher

Numbers seen in rapidly growing VS

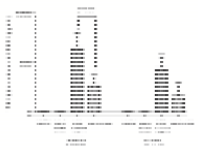
deVries et al, Otology Neurotology 2013



Slide 28

L-NAC: N-Acetylcysteine

Case control study of steroids +/- N-acetylcysteine: total hearing recovery in 41% steroids + NAC vs. 24% steroid alone ($p<0.05$)
No difference in some hearing recovery or serviceable hearing recovery
Noticeable differences specifically at 4000Hz when NAC used *Angeli et al, April 2012, Acta Otolaryngol*
35 patients w/ SSNHL randomized to NAC v steroid: 91% recover w/ NAC, 57% w/steroids *Chen 2017 Acta Otolaryngol (epub 2016)*



Pathak, Stern & Vambutas, Immunologic Research, 2015

NAC is inexpensive, OTC with a minimal side-effect profile

Slide 29

BUT IN MENIERE'S, IS IT JUST AN ELECTROLYE IMBALANCE, OR IS THERE IMMUNE DYSREGULATION?

ENDOLYMPH: HIGH K+, LOW NA+
PERILYMPH: LOW K+, HIGH NA+

First line management of Meniere's management is reduction of sodium salt Glucocorticoid receptors stimulate absorption of sodium (Pondugula 2006 Physiol Genomics)
Low salt diet in rat model increased Na+K+ATPase levels in stria vascularis (stria and vestibular dark cells secrete endolymph)(teCate 1994 Eur Arch Otorhinolar)
The Endolymphatic Sac is thought to be antigen processing of the inner ear inc TLR4 & 7 (Moller Laryngoscope 2015)
Passive transfer using an inner ear antigen result in ELH in both donor & recipient(Ikezono et al Audiol Neurotol 2000)
Donor T cells injected in peripheral circulation can proliferate in ELSE (Iwai Ann ORL 1999)

Slide 30

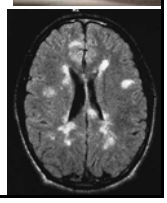
Sodium Concentration & Autoimmune Disease

Macrophages monitor tissue osmolarity & induce inflammation thru NLRP3; High dietary salt induces Th17 responses (Ip 2015 Nature Communications)
NaCl drives autoimmune disease by inducing pathogenic Th17 cells & incr TNF (Kleinewietfeld Nature 2013)
In EAE mice (animal model of MS) hi Na+ diet caused macrophage ingress & pro-inflammatory cytokine production (Hucke 2016 J Autoimmun)
Increasing dietary salt inhibits FOXP3+ regulatory T cells (thru SGK1) (Hernandez & Hafler 2015 JCI)
IL-1 upregulates the sodium dependent glucose transporter GLUT1 which induces neuronal cell death (Jurcovicova, Endoc Regul 2014)
Neuroinflammation from dietary salt may be genetic and sex specific: in mice **high salt diet exacerbated Th17 cell development & blood-brain barrier permeability** (Krementsov 2015 FASEB J)

Slide 31

Sodium Concentration and Autoimmune Disease

In Multiple Sclerosis **neuroaxonal loss related to intracellular sodium accumulation**
Higher sodium concentration was seen in T1 hypointense lesions of MS patients and higher concentrations seen in patients with greater disability (Paling et al, Brain 2013)
In a cohort of 70 patients with relapsing-remitting MS, **positive correlation between exacerbation and sodium intake**: 2.75 fold and 3.95 fold exacerbation rate in the medium and high Na+ groups compared to lo intake (Farez 2015 J Neurol Neurosurg Psy)
No correlation seen in pediatric onset MS (cohort of 170) (McDonald 2016 Mult Sclerosis Rel Disord)



Slide 32

Meniere's and environmental triggers: the allergy/immunology connection: *first described by W.W. Duke in 1923*

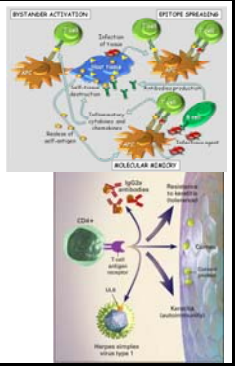
In a survey of 734 pts with MD, 59% reported airborne allergy 40% food allergy 37% positive skin testing (Derebery ONHS 2000)
Mold extract results in release of TNF from PBMC of MD patients (Frejo Scientific Reports 2018)
Aspergillus sequence homology to cochlin – drives cross-reactive Th17 Cells (Pathak & Vambutas 2013)
Prick testing in 48 atopic MD patients: post provocation, 30 had tinnitus and aural fullness and 6 had vertigo: ECOG positive in 29% pre & 78% post-test. (Topuz Adv Ther 2007)
Study of 5 atopic MD patients: 3 had >15% increase in SP/AP post challenge, (Eaton Laryngoscope 2003)
Similarly 4/7 exhibit >15% increase in SP/AP post challenge (Gibbs 1999 OHNS)

Slide 33

Mechanisms of autoimmunity

Molecular mimicry: viruses, and bacteria can induce autoimmunity via molecular mimicry ie:
group A strep to rheumatic fever;
infectious mono to ITP
Humoral autoimmunity
T cell mediated autoimmunity
Environmental insults: minocycline to SLE

Autoantibodies occur from apoptosis, antigen modification or cross-reactivity – antigen recognized by autoantibody triggers various TLRs or NLRs



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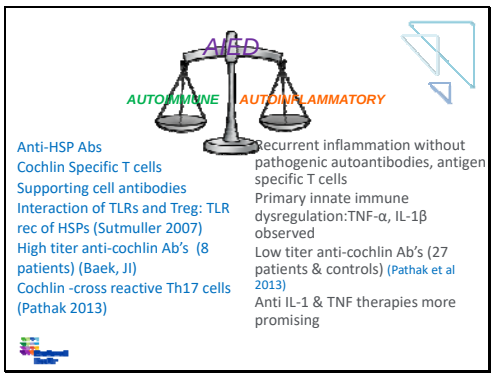

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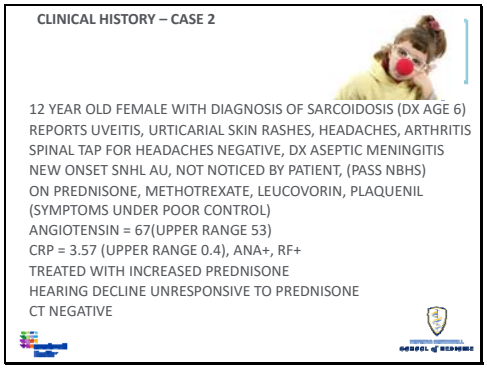

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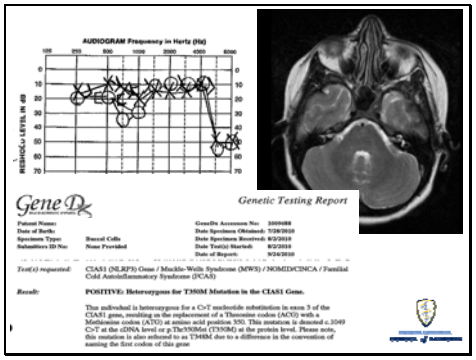

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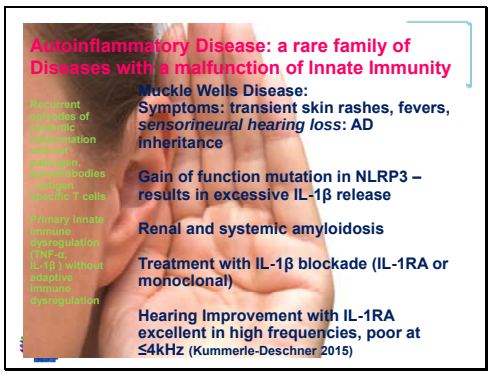

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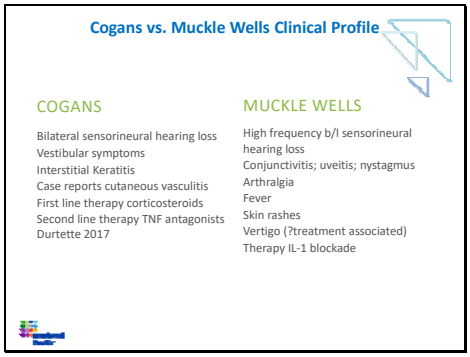

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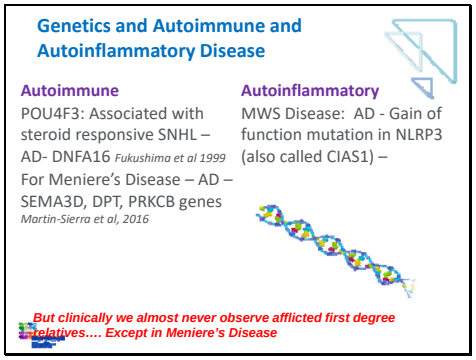

Slide 40

Hearing in Autoinflammatory Diseases

In a series of 57 CAPS patients: SNHL worse in higher frequencies, present in 23 (61%) NOMID, 10 (71%) NOMID/MWS, & 4 (33%) MWS ears
CHL in 4 (11%) NOMID ears and mixed hearing loss in 5 (13%) NOMID and 2 (14%) NOMID/MWS ears *Ahmadi N, 2011*
Series 33 MWS: 67% b/l progress SNHL, no vestib dysftn
IL-1 inhibition results in reduction of HL progression, but rare improvements *Kummerle-Deschner 2013, Arth Rheum*
In 23 MWS pts: 91% have HF SNHL, 70% affected from 500-4kHz, 24% improve on IL-1 inhibition *Kummerle-Deschner 2015*

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Autoinflammatory Neurologic Manifestations

Patients with milder CAPS disease have headache, migraine, papilledema, optic disc atrophy: Twelve of the 13 patients (92%) had headache, of whom 10 (77%) had features of migraine. Seven patients (54%) had sensorineural deafness. Nine patients (69%) reported myalgia. Six patients (46%) had papilledema and a further 2 (15%) had optic disc pallor. MRI brain scan was normal in all patients.
• Kitley et al Neurology 2010
Hearing loss in NOMID is caused by cochlear inflammation which can be visualized on contrast-enhanced fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) Aseptic meningitis and increased intracranial pressure are common, and permanent brain damage includes ventriculomegaly due to increased intracranial pressure and brain atrophy

Slide 42

Pattern of inflammatory parameters in MWS patients carrying the *NLRP3* E311K mutation

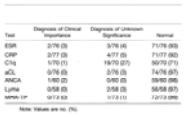
From Kuemmerle-Deschner, Arthritis Res Therapy 2011

	Number of individuals (%) with elevations and associated levels
Classical inflammatory markers (normal)	
Elevated ESR (< 22 mm/h)	
Number (%)	7/13 (54%)
Mean mm/h (stdv)	31 (20-55 mm/h)
Elevated CRP (< 0.5 mg/dl)	
Number (%)	13/13 (100%)
Mean (stdv)	2.25 (0.66-5.6)
Interleukin-1 (IL-1) (< 5 pg/ml)	
Number(%)	0/8 (0%)
mean (range)	0.52 (0.2-1.48)
Interleukin-6 (IL-6) (< 5 pg/ml)	
Number (%)	5 (38%)
mean (range)	6.37 (5.9-15.7)
Tumor necrosis factor α (TNF-α) (< 8 pg/ml)	
Number (%)	7 (54%)
mean (range)	9.37 (8,2-16.5)

CRP in acute hearing disorders

Hs-CRP 0.461±1.335 mg/dL in SSNHL and 0.129±0.125 mg/dL ctrls
Gode 2017 J Int Adv Otol

No difference in Japanese cohort:
Masuda 2012 Otol Neurotol



Hirose 1999 Laryngoscope
****not all patients with SSNHL***

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Patient	Status	Autoimmune History	Hearing History	PTA & HINT	Serology
40 y/o female[1,2]	Control (birth anoxia?)	None	Congenital loss – non progressive	PTA 100dB; HINT 60dB quiet: 0%	NP*
49 y/o male[1,2]	Control	None	40+ years loss	PTA 100dB; HINT 50dB quiet: 10%	NP*
79 y/o female[1-3]	Control (LVA)	None	70+ years LVA	PTA 110; HINT 55dB quiet: 0%:	NP*
1.5 y/o female[2,3]	Control (Cx 26)	None	Congenital – stable	PTA: NR 102dB ABR; IT-MAIS: 12%	NP*
36 y/o female	AIED, progress loss	Rheum Arthritis	29 years, periods of rapid loss	PTA 120dB; HINT: 55dB quiet: 0%	P0, RF IgM (14.2) & IgG (25.3), ANA 1:1280 (HEp-2), IgM phospholipids (10.9), IC (26.1)
56 y/o male[1,2]	AIED, rapid loss	Type I IDDM	2 years, rapid loss	PTA 120; HINT 70dB quiet: 0%	ANA 1:1280 (mouse kidney), ANA 1:320 (HEp-2),weakly +IgM phospholipid Ab (12.1)
58 y/o female[1,2,3]	AIED, rapid loss	Hashimoto thyroiditis	4 years, rapid loss	PTA 110dB; HINT at 50dB quiet: 0%	Borderline IC (21.4), weakly + IgM phospholipids (11.7), borderline RF IgG (20.8)
51 y/o female[2,3]	AIED, progress loss	None	Sudden loss AS 10 yrs ago sudden loss AD <6 mos	PTA 80dB; HINT 65dB quiet: 19%	68kD positive
3[illegible]male[2,3]	AIED, b/l rapid SNHL	None	6 months, rapid loss	PTA 120dB; IT-MAIS 8%	Negative

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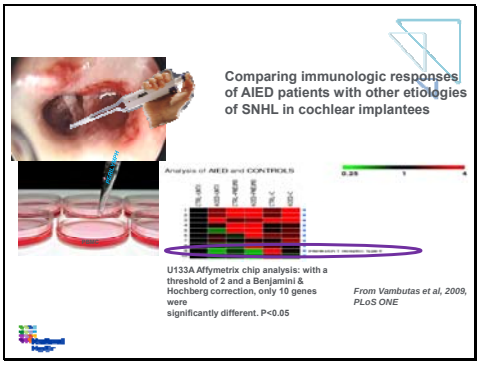

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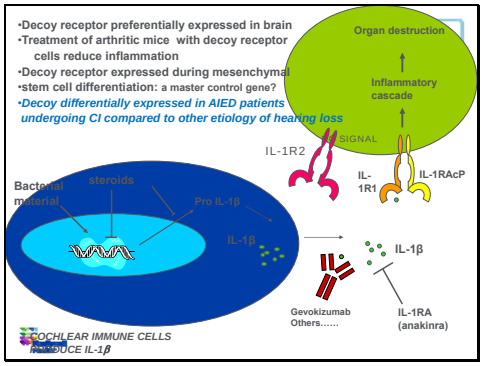

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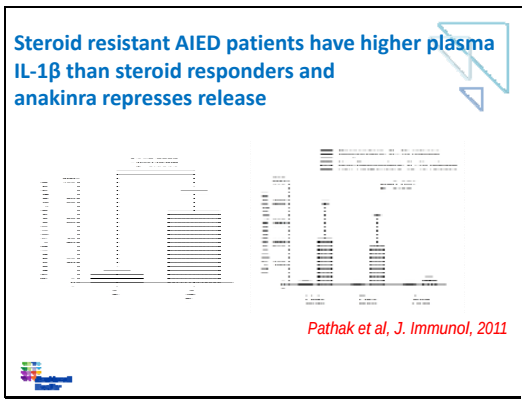

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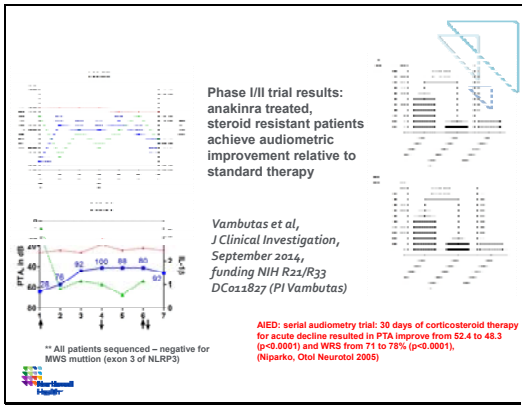

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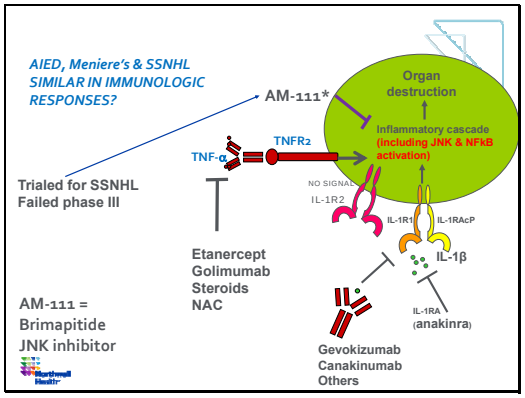

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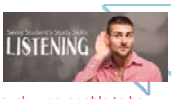
Case #1 ***Case 1: What happened to our patient?***



Clinical Course over 6 years:

- Placed on prednisone – continuously – never able to be tapered – IT steroids also used – TM perf
- Fluctuation in hearing with strong correlation to steroid dose
- Autoimmune etiology strongly suspected, placed on methotrexate
- Unable to wean methotrexate, every attempt – increased HL
- Started on Anakinra
- Finally able to wean steroids & methotrexate without relapse – preserved his hearing thresholds
- Switched to Ilaris – last seen – graduate of Ivy League Institution, rejected his hearing aids, IN law school now

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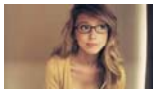
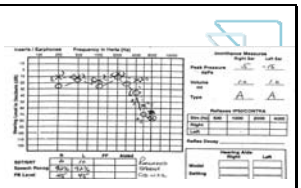
Case 2: What happened to our patient?





Treated with anakinra initially –
Dramatic improvement in skin, ocular findings, joint pain
Switched to Ilaris at 1 year, other meds: none
Mild progression of SNHL
CRP=0.14

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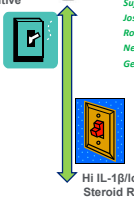
HYPOTHESIS:
Hi TNF/low IL-1β:
Steroid Sensitive



Hi IL-1β/low TNF:
Steroid Resistant

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Questions???? Please use the CHAT function!
All questions are good ones!