Autoimmune Ear Disorders and Endocrine disorders affecting the audiovestibular system

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Autoimmune ear disorders

Primary AIED

- The autoimmune assault is directed to the ear specifically the cochlea or the vestibule only
- Can be due to a cytokine mediated innocent bystander reaction or a cross reaction to an event or intolerance or genetic factors
- May cause an endarteritis and hyperviscosity by the circulating antigen antibody complex deposition and/or auto reactive T cells
- Endogenous reactive proteins include cochlin, tectorin, tyrosine phosphatase, connexion 26
- A third of all endolymphatic hydrops associated with autoimmunity
- May follow trauma or non specific infection in the ear
- Mechanism follows the biochemical cascade
- A third may develop other systemic autoimmune disorder

Secondary AIED

- Much more heterogenous presentation than the adult population and may be under diagnosed; high index of clinical suspicion
- A person presenting with features of systemic auto immune disorder with either hearing or balance problems or both should raise a strong suspicion for AIED
- Autoantibodies in specific pathologies are cochleovestibular toxic
- Variable hearing losses with 30-50% vestibular involvement
- Immunosuppressant salvage of audiovestibular function possible

- Vogt Koyanagi Harada syndrome
- Cogan’s syndrome
- Sjorgen’s syndrome
- SLE
- Antiphospholipid syndrome
- RA
- Anti cardiolipin syndrome
- Sarcoidosis
- Relapsing polychondritis
- Myasthenia gravis
- Psoriasis
- Ankylosing spondylitis
- Polyarteritis nodosa
- Wegener’s granulomatosis
- Systemic sclerosis
- Goodpasture syndrome
- Behcet’s disease
- Hashimoto’s thyroiditis
- Dermatomyositis
- IBD
- GBS
- Polymyositis
- Coeliac disease

Clinical features

- Usually and invariably sensorineural hearing loss
- May be sudden (RP 0.7 to 1.8/100,000, increases with increasing age)
- May be rapidly progressive over months (RP 2.6% of all hearing impaired children)
- Low and mid frequencies but may be high frequency or flat and fluctuating and may be asymmetrical
- 40% respond to steroids
- 50% with vestibular weakness
- Prognosis depends on degree of hearing loss and associated vestibular problems and the timing of steroids

Diagnosis

- Typical presentation of cochleo-vestibular affliction
- Full audiovstibular examination and investigations to exclude the other differentials; must consist of imaging
- Screening ESR and CRP
- Autoimmune markers :
    - Serum immunoglobulins (IgM, IgG, IgA, IgE)
    - Anti-thyroid antibodies
    - Antinuclear antibodies (ANA)
    - Antineutrophil cytoplasmic antibody (ANCA)
    - Antiendothelial cell antibody (AECA)
    - Anti-phospholipid/anti-cardiolipin antibodies
    - Rheumatoid factor/anti mitochondrial antibody/C3 and C4

Research on marker for primary AIED

- Anti HSP 70 not very sensitive as shared with conditions like Lyme's disease
- ELISPOT test for T cell ILN – γ
- Anti CL2 antibody not commercially available
- Antibody to myelin protein P0 in cochlea has shown promise

Management

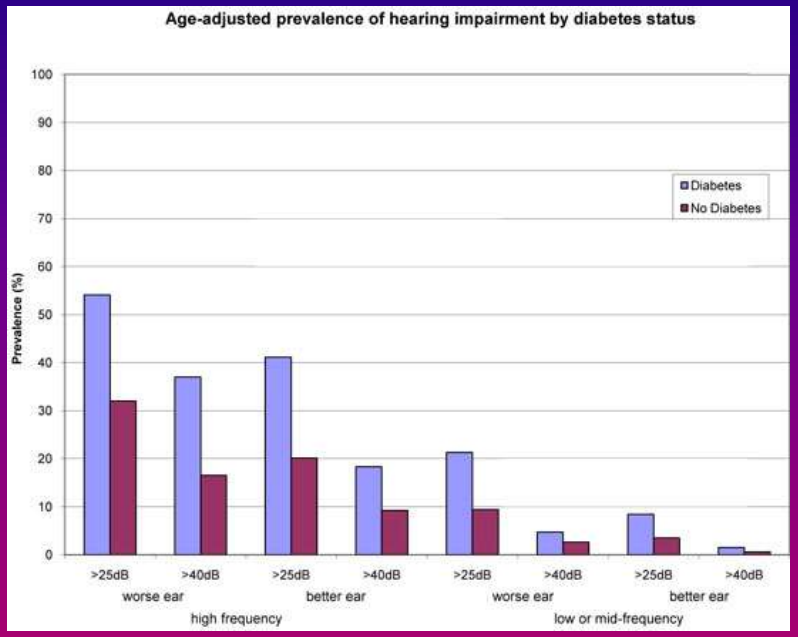
- In the acute active phase, corticosteroids remain the mainstay of treatment tapered over 2 -4 weeks
- In the stabilised phase, role of corticosteroids is anecdotal and may be tried to pre-empt symptoms progression
- Side effects to steroids in 15%
- Cyclophosphamide, methotrexate and immunomodulators like anti TNFα; Rituximab may be tried
- Plasmapheresis in severe cases not responding to other immune suppressants
- Intra tympanic steroids in resistant cases
- Audiovestibular rehabilitation and treatment of primary condition
- Evidence is sketchy and each case must be carefully evaluated

Conclusions

- Diagnosing hearing loss and balance disorders in children is challenging, stimulating and rewarding as it is so complex especially when associated with other rare organ pathology
- Managing AIED is difficult and there is limited evidence on diagnosis and management and awareness is crucial
- Intervention makes a significant difference in many children's and parents' lives and recognition is crucial
- Is very much holistic and multidisciplinary – we are essentially treating not just the hearing loss or the balance disorder but the child as a whole and indirectly the parents

Endocrine disorders and audiovestibular involvement

Diabetes and hearing impairment (ASHA 2014)



- Usually in Type 1
- Vascular origin
- May be sudden
- Linked to glucose control (HbA1c) and to creatinine
- Mild symmetrical mid and high frequency loss

The diabetes – deafness syndromes

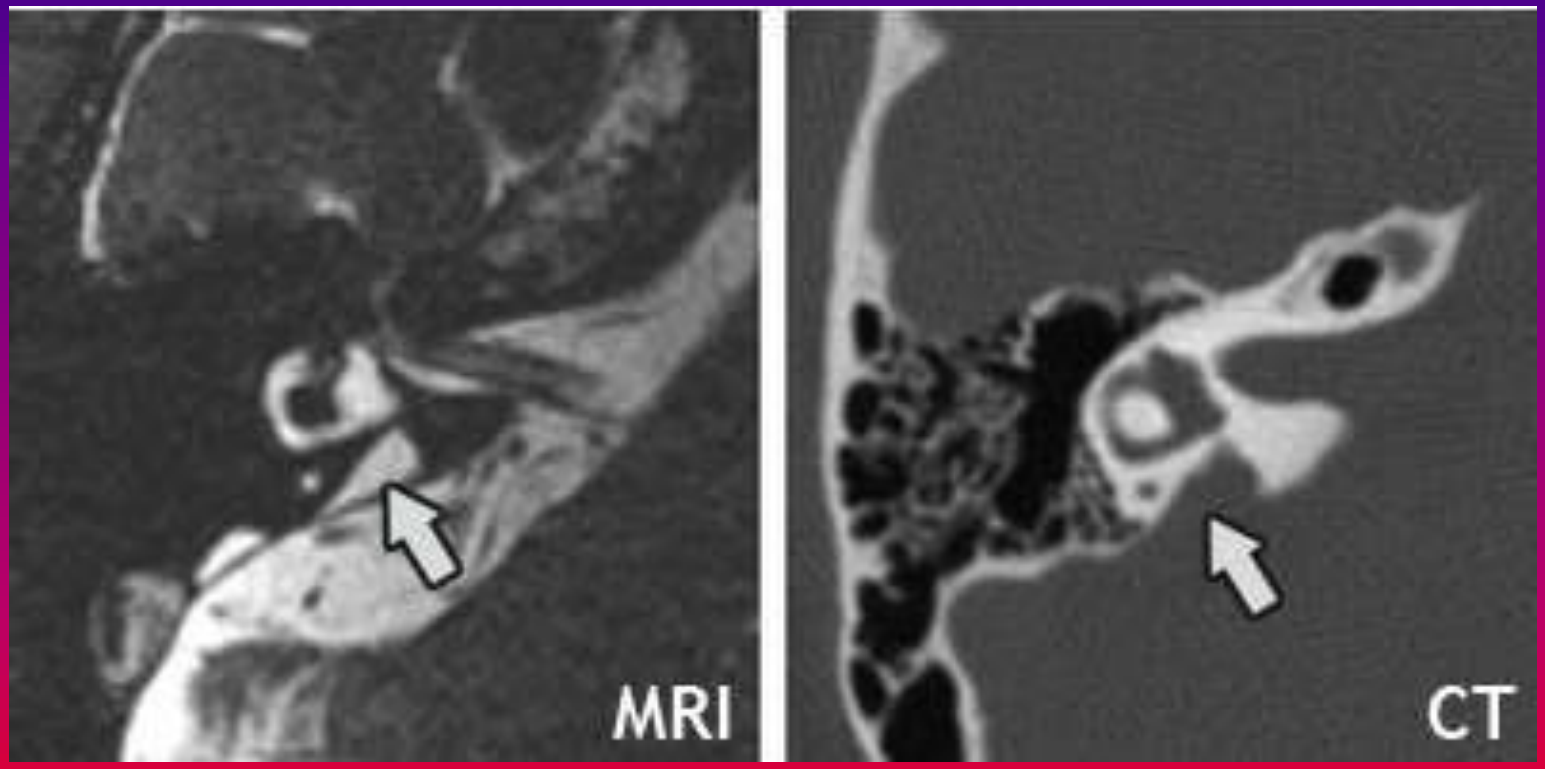
Condition	Inheritance	Manifestation
Maternally inherited diabetes and deafness MIDAS – Ballinger Wallace	Mitochondrial; 3243 tRNA; may be associated with MELAS	Late teens; severe to profound high frequency SNHL
Diabetes insipidus Diabetes Mellitus Optic atrophy and Deafness DIDOMOAD - Wolfram	Autosomal recessive 4q or mitochondrial 6466 tDNA; CSDI2 gene	Congenital or early childhood; progressive high frequency severe SNHL
Thiamine responsive megaloblastic anaemia syndrome TRMA - Rogers	Autosomal recessive 1q; SLC19A2 gene	Infancy to childhood; mild to profound flat SNHL
Rod cone dystrophy, hearing loss, type 2 diabetes, obesity and cardiomyopathy syndrome - Alstrom	Autosomal recessive; ALMS gene	Early childhood progressive severe to profound SNHL

Thyroid disorders and hearing loss (Hashemipour 2012)

- Thyroid hormones are essential for fine balance between oxygen radicals and scavengers in the apoptotic pathway of OHC; the beta receptor mediated action for myleinogenesis of VIII nerve
- 3-25% congenital hypothyroid children have low and mid frequency SNHL
- 50% of autoimmune thyroid conditions associated with audiovestibular problems usually endolymphatic hydrops
- Non auto immune hyperthyroid conditions can cause a SNHL by their sympathetic stimulation of cochlear vasculature but the link is tenuous
- AI thyroiditis can present with sudden SNHL
- AIED may be reversible with good thyroid control

Pendred's syndrome

- Commonest syndromic HL in children; 10% of congenital deafness
- Progressive flat SNHL or fluctuating mixed loss with dilated vestibular aqueduct and diffuse thyroid enlargement
- Autosomal recessive and mapped to chromosome 7q with SLC26A4 mutation (the Pendrin gene)
- Compensated euthyroid state with defects in thyroid discharge on perchlorate challenge; raised TRH response and thyroglobulin
- Head trauma must be avoided for sudden drop in hearing


MRI
CT

The parathyroid and the ear

Condition	Inheritance	Manifestation
Barakat – HDR	Autosomal dominant GATA 3 in 10q	Hypoparathyroidism with early childhood SNHL; *first congenital HL identified Alder Hey 2014*
DiGeorge - velocardiofacial	Autosomal recessive 22q TBX1	Hypoparathyroidism with conductive HL and ossicular problems
The 10p DiGeorge phenotype	Sporadic 10p interstitial or terminal	Hypoparathyroidism with SNHL
Yumita - HPHL	Unknown probably same as HDR	Early childhood moderate SNHL and hypoparathyroidism only

- Hypocalcaemia due to any reason affects the integrity of the gravitational otoliths (Dasgupta and Witana 2010)

The pituitary and the cochleovestibular apparatus

- Growth hormone has been shown to be a modifier of the apoptotic pathway of hair cells in the inner ear (Schuck et al 2011)

Condition	Inheritance	Manifestation
CAGSSS syndrome (Schwartzentruber 2014)	Autosomal recessive IARS2 1q	Cataract, GH deficiency, sensory neuropathy, progressive early SNHL and skeletal dysplasia
Combined pituitary deficiency – Winklemann syndrome	LHX3 9q	Childhood SNHL with asexual dwarfism and rigid cervical spine
GH resistance – Laron's syndrome	Autosomal dominant	Hypoglycaemia, raised GH but with low IGF and IGFBP3 and early childhood SNHL

- Sufficiently large functioning or non functioning pituitary tumours may directly compress the VIII nerve

The gonadal syndromes and hearing loss

Condition	Inheritance	Manifestation
X linked CAH (Zachmann 1992)	Xp DAX1 mutation	Progressive SNHL; congenital adrenal hypoplasia and hypogonadotropic hypogonadism
Perrault syndrome	HSD17B4 5q autosomal recessive	Early SNHL and ovarian dysgenesis
Idiopathic hypogonadotropic hypogonadism (IHH) with anosmia (Kalmann syndrome) or normosomic IHH	KAL1 in Xp mutation probably recessive or SOX10 like Waardenburg syndrome	Variable SNHL and corpus callosal agenesis with synkinesia
Growth mental deficiency syndrome - Myhre syndrome	SMAD4 18q, sporadic	Skeletal abnormalities and cryptorchidism with variable SNHL

Turner's syndrome

Meta analytic study exploring hearing loss in Turner's syndrome (Dasgupta 2009):

- OME in 60.9%; CHL/mixed loss in 26.4% and SNHL in 39.9%; normal hearing in 30.9%
- Given the above prevalence, active management of hearing status is important
- Following diagnosis, information about hearing needs to be disseminated

Conclusions

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- Intervention makes a significant difference in many children's and parents' lives and recognition is crucial

- Is very much holistic and multidisciplinary – we are essentially treating not just the hearing loss or the balance disorder but the child as a whole and indirectly the parents