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E-Book

Auto-Immune Inner Ear Disorders: Unheard Dangers

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"Surviving in a body that wants to destroy you??

It ain't easy trying to survive when you're physically destructing from inside out".

Foreword

One reason that steered me fanatical to pen down this module happens to be that it greatly affects large section of population and causes irrevocable damages. The time is not far that it will become common like Diabetes and Hypertension but the incurred damage would not be easy to reverse; impacting the persons' lifestyle, mental and physical health.

This module tends to answer all the associated queries that arise out of the patient's or treating clinicians' mind as a result of inquisitiveness.

The module has four distinct sections for better illustration of the content.

Section-1 named the conditions involving AIED has description of conditions involving AIED; including their signs and symptoms, Aetiology, Associated effects on hearing, vestibular and overall health.

Section-2 named what is auto-immunity? Enunciates the dynamics of auto- immunity and immune tolerance.

Section-3 named what is auto-immune inner ear disorders will give a basic idea about what is AIED, its aetiological factors, clinical manifestations, diagnostic formulation, classification of AIED (six sub-types), proposed methods for clinical intervention, end note discussion.

Section-4 named effects of auto-immunity on hearing and vestibular health has vindication on the effects of auto- immunity on hearing and vestibular (balance) well being. This section will give readers an idea of possible effects of AIED and its correlation with hearing and vestibular health.

We hereby hope that this module should be able to apprise the people that what all are the reasons for their condition, how to avoid them and moreover what should be the solution.

We as clinicians always tend to keep on ascertaining yet better ways to help our patients and hence would like to give our patients most of credits because without their valuable feedback we would have never been able to prepare this module.

Enjoy Reading!!!

Seejal Shrest

Conditions involving auto-immune inner ear disorder(s)

Rheumatoid arthritis: Chronic inflammatory disorder of auto-immune nature affecting joints (mainly hands and feet). Usually, same joint on both sides of body is affected. It has deposition of immune complex(es) in the hair cells of inner ear and fluid of middle ear causing mixed or sensori-neural hearing loss of mild to moderately severe degree.

Figure 1: Stage of rheumatoid arthritis.

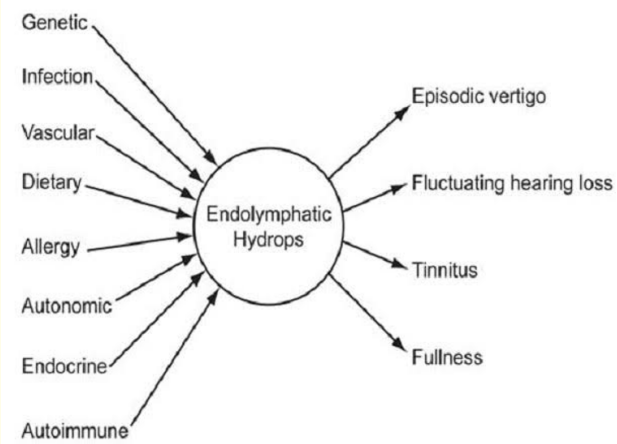

Figure 2: Cause and effects of endolymphatic hydrops.

Meniere's disease or endolymphatic hydrops: Inner ear disorder attributed to excessive endolymphatic fluid pressure in the membranous labyrinth causing the Ressiner's Membrane to become distended. Many causes have been proposed and it is generally thought to be associated with problems regulating the production of Endolymph or a blockage of the Endolymphatic Duct and Sac. It has been attributed to many different causes such as food allergies, hypothyroidism, adrenal and pituitary gland insufficiencies, auto- immune disorders, vascular disease, stenosis of the internal auditory meatus, trauma, syphilis, viral infections etc. Clinically it is characterized by episodic attacks of vertigo, hearing loss, tinnitus and feeling of pressure or fullness in the ears. Attacks last for a minimum of 20 minutes to a maximum of few hours. The symptoms fluctuate; hearing loss and tinnitus often reduce between attacks and may even resolve completely between attacks in the early stages. However, the long term trend is in the direction of constant hearing loss and tinnitus, which worsens during the attack. It is possible that the loss gradually progresses to Profound. The two variants of this condition are:

- Cochlear Meniere's disease when the symptoms don't include vertigo.

- Vestibular Meniere's disease when the symptoms don't include hearing loss.

Gut-dysbiosis: It simply means imbalance of microbes in the gastro-intestinal tract. Symptoms include frequent built up of gas, bloating, belching, loose stools, diarrhoea, constipation, acidic reflux, unexplained weight loss or weight gain, irritable bowel syndrome (IBS), irritable bowel disorder (IBD), anxiety, depression and/or frequent low mood, chronic bad health, joint pain, brain fog, dermatological issues (eczema, psoriasis, acne), low energy and chronic fatigue, allergies and/or food sensitivities, chronic yeast or fungal infection. It is auto-immune in nature as the increased number of bad (opportunistic) bacteria will disturb the natural fauna of the body and increase the synthetic micro-biome making the person more susceptible to various kinds of irreversible conditions. Surprisingly the alterations can harm the entire body and hence inner ear is no exception; from nervous system to digestion; mood based disorders to depression. In short, gut-dysbiosis is an inevitable by-product of modern lifestyle and current state of food habits. Associated hearing loss can be mixed or sensori-neural of degree mild to profound because the opportunistic microbial population will start to attack the fluid of middle ear and cochlea of inner ear.

Brain fog: It is not a medically recognized term but a commonly used phrase that sums up feelings of confusion, forgetfulness, lack of focus and mental clarity. It is fairly common but not normal. Causes fall mainly under three main categories inner ear, lifestyle related, side-effect of a condition and medication. The involved hearing loss is caused by conductive, mixed or sensori-neural components; with degree ranging from mild to severe depending on site that is affected and for what duration has it been affected; its

Figure 3: Driving forces of gut-dysbiosis.

Figure 4: Gut-immune cycle.

Figure 5: Causes of brain fog.

starts from mild conductive and may gradually progress upto severe sensori-neural hearing loss.

Vestibular asymmetry: Pathological Vestibular Asymmetry can be divided into static and dynamic types. Static Asymmetry results from a unilateral change of the resting neural input. Acute, Chronic, Recovery stages can be recognized if one interprets the direction and intensity of the resultant spontaneous nystagmus relative to the clinical picture. Static Asymmetry is additive with induced Asymmetry and manifests itself as directional preponderance or as the direction-fixed or direction-changing feature of positional Nystagmus. Dynamic Asymmetry refers to abnormal asymmetry induced by normal head movements. E.g. in case of unilateral hypofunction, greater gain is observed with head movement towards the unaffected side suggesting non-linearity. Visually induced vestibular asymmetry is a form of dynamic asymmetry generated by convergence of visual-vestibular information, causing symptoms in certain motion-active visual environments. Hearing loss incurred is mild to severe mixed or sensori- neural as there is alteration in fluid composition of middle or inner ear.

Relapsing polychondritis or the Red ear syndrome: It is a rare chronic cartilage disorder in which the cartilage of different parts of body gets inflamed frequently. Some of the cartilages which get inflamed are present in tissues of the ears, nose, spine and trachea, but it can also affect the eyes, heart and even the overall circulatory system. The root cause of the same is still unveiled but it is suggested that it may be due to a compromised immune system of body causing recurrent inflammation of various tissues of body. Associated hearing loss is conductive, mixed or sensorineural in nature; with degree ranging from mild to profound depending upon the part affected and its severity.

Figure 6: Visual appearance (of one kind) of ear of a person having Red ear syndrome.

Systemic lupus erythematosus: It is a chronic disease that causes inflammation in connective tissues such as cartilage and the lining of blood vessels which provide strength and flexibility to structures throughout the body. Symptoms vary among the affected people and can involve many organs and systems, including skin, joints, kidneys, lungs, central nervous system and blood forming (Haematopoietic) system. It may appear first as fatigue, a vague feeling of discomfort or illness (malaise), fever, loss of appetite, weight loss. Most of the affected individuals also have joint pain, typically affecting same joint on both sides of the body, muscle pain and weakness. Dermatological issues are common, a characteristic feature is a flat red rash across the cheeks and bridge of the nose called butterfly rash (due to resultant shape formed). Other skin problems include calcium deposition under skin (Calcinosis), damaged blood vessels in skin (Vasculitis), tiny red spots (Petechiae), Hair loss (Alopecia), Open sores (Ulcerations) in the moist lining (mucosa) of the mouth, nose or less commonly the genitals (private parts). About one-third of the sufferers also develop kidney disease (Nephritis), Heart problems may also occur. The inflammatory characteristic can also damage the nervous system and may result in abnormal sensation and weakness in the limbs (Peripheral Neuropathy), Seizures, Stroke and difficulty in processing, learning and remembering the information (Cognitive Impairment). Anxiety and depression are also common. Overall SLE gradually gets worse over time and damage to major organs can be life-threatening. Associated hearing loss is mild to severe mixed (when structures of both inner and middle ear get affected) or sensori-neural (when only inner ear structures such as spiral ganglion, hair cells are affected).

Figure 7: Symptoms of SLE.

Polyarteritis nodosa (PAN) or systemic necrotizing vasculitis: It consists of focal, inflammatory and arterial nodules. Main feature is that the inflammation is throughout the entire arterial wall. Most cases occur in 4^{th} or 5^{th} decade of life, although it can occur at any stage. Men are twice as likely to be affected as women. A minority of patients have an active Hepatitis B infection, but in rest of the cases the cause is still unknown and the disease is said to be idiopathic in nature. It is a multisystem disease that presents with fever, sweats, weight loss and severe muscle and joint aches/pain. It may develop in sub-acute fashion, over several weeks or months. Patients may have non-specific complaints such as fever, malaise, weight loss, anorexia and abdominal pain. It can affect nearly any site in body, but has a pre-disposition for organs such as skin, kidneys, nerves, gastrointestinal tract, heart, eye and genitals. Many patients have high blood pressure, elevated Erythrocyte Sedimentation Rate (ESR), skin anomalies (rashes, ulcers), peripheral neuropathy. Associated hearing loss could be mild to severe mixed (when arteries and muscles of middle and inner ear affected) or sensori-neural (when only arterial supply of inner ear is affected).

Lyme disease: It is an infectious bacterial disease spread by ticks. Classic early signs of an infection are rash in shape of bull's eye or fever. If not treated in early stage, it can spread to blood stream

Figure 8: Symptoms of PAN.

and cause neurological problems such as meningitis, loss of muscle tone in face, memory loss, sleep disturbances and mood changes. It can cause even more damage to body including Auditory system; whose effects include hearing loss (mild to severe sensori-neural as mostly inner ear structures are affected), Hyperacusis, Tinnitus. An estimated 48% of patients with late-stage Lyme diseases may develop hearing issues.

Figure 9: Symptoms of lyme disease in acute v/s chronic stages.

Churg-Strauss syndrome (CSS): It is also called eosinophilic granulomatosis with polyangiitis (EGPA) or allergic angiitis and granulomatosis or allergic granulomatosis or allergic granulomatosis and angiitis or Churg- Strauss Vasculitis. It is a rare disorder that may affect multiple organ systems, especially lungs. It is characterised by abnormal clustering of certain white blood cells (hypereosinophilia) in the blood and tissues, inflammation of blood vessels (vasculitis), the development of inflammatory nodular lesions called Granulomas (Granulomatosis). Most of the affected individuals have a history of allergy, Asthma and other associated lung (pulmonary) abnormalities often precede the development generalized (systemic) symptoms and findings are observed in as little as six months or as late as two decades. Non-specific findings typically include flu-like symptoms such as fever, a general feeling of weakness and fatigue (malaise), loss of appetite (anorexia), weight loss, muscle pain (myalgia). Additional symptoms and findings vary depending upon the specific organ systems affected. The nerves outside the central nervous system (peripheral nerves), kidneys, and gastrointestinal tract are often involved. Serious organ damage and potentially life threatening complications may result. Although the exact cause is unknown, many researchers indicate that abnormal functioning of the immune system plays a crucial role. Symptoms may include ulcerations of the mucosal membrane in nose with secondary bacterial infection, persistent runny nose, sinus pain, chronic middle ear infection (otitis media) potentially resulting in mild to severe mixed hearing loss (there are numerous other symptoms).

Figure 10: Features of Churg-Strauss syndrome.

Vestibular aqueduct syndrome: Also called as large vestibular aqueduct disorder or large endolymphatic sac anomaly and it refers to the presence of congenital sensori-neural hearing loss with an enlarged vestibular aqueduct due to enlargement of the endolymphatic duct. It is thought to be one of the most common congenital causes of senrori- neural hearing loss that is sudden and progressive after a minor head trauma. Associated anomalies

include Pendred syndrome, vestibular anomalies, cochlear anomalies (Cochlear Hypoplasia/Mondini's Dysplasia), semicircular canal anomalies. Usually it presents with moderate to Profound mixed or sensori- neural hearing loss due to altered fluid composition of middle or inner ear.

Figure 11: Enlarged vestibular aqueduct.

Endocrine hypertension: It is a subset of hypertension caused by hormonal imbalance. Patients who develop it before the age of 30 years have strong family history of hypertension, adrenal tumours, or develop low potassium levels (Hypokalemia). They should get screened for endocrine hypertension. It can be caused when glands produce too much or not enough hormone, or when they are affected by tumours. Its types include Primary aldosteronism (including Conn's Syndrome, Bilateral Adrenal Hyperplasia, Primary Adrenal Hyperplasia, Glucocorticoid remediable Aldosteronism (GRA), Familial Hyper Aldosteronism), Cushing's Syndrome, Pheochromocytoma, Acromegaly, Hyperthyroidism or Hyperthyroidism, Other forms (Pseudohypoaldosteronism type 2 or Gordon's Syndrome, Liddle's Syndrome, Apparent Mineralocorticoid excess, Licorice Ingestion, Bartter's Syndrome, Gitelman's Syndrome). Hearing loss associated could be anywhere from mild to severe conductive, mild to Profound mixed or sensori-neural depending on what part of ear has been affected and for how long. It may start from mild conductive hearing loss and keep fluctuating and may progress to severe to profound sensori- neural hearing loss.

Charcot-Marie tooth disease: Also called as Hereditary Motor and Sensory Neuropathy (HMSN) or Peroneal Muscular Atrophy. It comprises of group of disorders that affect peripheral nerves (Peripheral Neuropathies). It affects both motor and sensory nerves (motor nerves cause muscles to contract and control voluntary activities such as speaking, walking, breathing and swallowing). A typical feature includes weakness of lower limbs resulting in foot-drop and high stepped-gait with frequent tripping or falls. Foot deformities such as high arches and hammer-toes (middle joint of toe bends upwards) are also characteristics due to weakness of small muscles in the feet. Lower limbs may take on an inverted champagne bottle appearance due to the loss of muscular bulk. Later in the disease, weakness and muscular atrophy may occur in hands, resulting in difficulty with carrying out fine motor skills (coordination of small movements usually in the fingers, hands, wrists, feet and tongue). Onset of symptoms is often in adolescence or early adulthood but some individuals develop symptoms in mid-adulthood. The severity of symptoms varies greatly among individuals and even among family members with the disease. Progression of symptoms is gradual. Pain can range from mild to severe and some people may need to rely on foot or leg braces or other orthopaedic devices to maintain mobility. In rarest of the rare case, individual may have respiratory muscle weakness. It is not a fatal disease and people with most forms of CMT have normal life expectancy. Associated hearing loss could be mild to severe sensori-neural or mixed depending on what structures of middle and inner ear are affected and up to what extent.

Figure 12: Features of Charcot Marie tooth disease.

Ankylosing spondylitis or Bechterew's disease: It is a form of arthritis primarily affecting spine, although other joints can become involved. It causes inflammation of the spinal joints (vertebrae) that can lead to severe chronic pain and discomfort. In more advanced cases this inflammation can lead to ankylosis inner ear. New bone formation in the spine causing sections of the spine to get fused in fixed, immobile position. It can also cause inflammation, pain, stiffness, in other areas of body such as shoulders, hips, ribs, heels, small joints of the hands and feet. Sometimes eyes can also be involved and though rarely lungs and heart also get affected. Hallmark feature is the involvement of Sacroiliac joints (joints located at the base of spine, where spine joins the pelvis) during the progression of disease. It is important to note that the course of Ankylosing Spondylitis varies greatly from person to person. So too can the onset of symptoms. Although symptoms usually start to appear in late adolescence or early adulthood (age range of 17 years to 45 years) symptoms can occur in children or much later in life. Hearing loss is usually moderate to severe mixed (when joints of middle ear are affected) or sensori-neural (when neural network between brain and ear is affected) in nature.

Figure 13: Features of ankylosing spondylitis.

Temporal bone trauma: The trauma is usually the result of blunt head injury and can result in damage to brain, meninges, facial nerve, middle and inner ear. Complications can include intra-cranial haemorrhage, cerebral contusion, Cerebrospinal Fluid (CSF) leakage, meningitis, hearing loss (that is mild to profound mixed or sensori-neural depending on site of lesion, and the severity of damage caused), vertigo and facial paralysis. Temporal bone trauma is usually the result of blunt head injury and patients commonly suffer from multiple other body injuries. Motor vehicle accidents are the most common cause, with falls and gunshot wounds contributing to lesser extent.

Ulcerative colitis: It is an inflammatory disease potentially affecting the entire large intestine (colon and rectum). Inflammation is confined to the innermost layer of the intestinal wall (mucosa). It can go into remission and then recur. Men and women are equally affected and people of all age groups can develop it. A family history slightly increases the risk of disease. The exact cause is unknown but it isn't contagious. Potential causes include immune system abnormalities and bacterial infection. Most patients develop symptoms in their 40s. A smaller number experience symptoms for the first time later in life (ages 60 years to 70 years). The symptoms are similar to Crohn's disease, when the later only affects the colon and rectum. The most common symptoms include abdominal cramping, pain, diarrhoea, bleeding with bowel movements, fever, fatigue, weight loss. Hearing loss is similar to Gut-Dysbiosis inner ear. mild to profound mixed or sensori-neural depending on what is the site of microbial attack and for what duration have the microbes been attacking.

Figure 14: Ulcerative colitis.

Scleroderma or systemic sclerosis: It is a rare and chronic connective tissue disease generally classified as one of the autoimmune rheumatic disease. Hardening of the skin is one of the most visible manifestations of the disease. The disease varies from patient to patient. It is not contagious, infectious, cancerous or malignant. Any chronic disease can be serious. The symptoms

vary greatly from person to person and the effects can range from very mild to life threatening, seriousness will depend on the parts of body affected and the extent to which they are affected. Prompt and proper diagnosis and treatment may minimize the symptoms of scleroderma and hence lessen the chances of irreversible damage. The exact cause is still unknown but it is known to involve an overproduction of collagen. Limited Scleroderma is sometimes called 'CREST' Syndrome CREST stands for the initial letters of 5 common symptoms Calcinosis; Reynaud Phenomenon; Esophageal Dysfunction; Sclerodactyly; Telangiectasia. Associated hearing loss could be moderate to Profound mixed or sensori-neural depending on where the collagen deposition has been more than optimal.

Figure 15: Types of scleroderma.

Psoriatic arthritis or inflammatory arthritis: It usually affects people who already have skin condition called psoriasis. This causes patches of Red raised skin, with white and silvery flakes. Sometimes people have arthritis symptoms before psoriasis. It can affect people of any age. Psoriatic Arthritis is a type of Spondyloarthritis. It can cause a number of symptoms around the body and the patient will often have two or more of these symptoms and they can range from mild to severe. One of the main symptoms is pain, swelling and stiffness because of inflammation inside a joint. Most commonly affected joints are of neck, back, shoulders, elbows, wrists, fingers, knees, ankles and toes. Joint stiffness is usually worse in the morning and it can last for more than 30 minutes. Person may also feel stiff after having rest period. People with this condition can have swollen fingers or toes (usually 1 or 2 at a time). It can also cause fatigue that is severe and persistent that can't be cured with rest. If the person is having genetic chances of getting this condition, triggers may be infection; accident or injury; obesity and smoking. It is not contagious, there is also an element of chance, and it might not be possible to say for certain what caused the condition. Involved hearing loss could be mild to moderately severe conductive (when only sound conduction pathway is affected), mixed (when middle ear joints also get stiff) or sensori- neural (when the inflammation is in inner ear).

Figure 16: Symptoms of psoriatic arthritis.

What is auto-immunity?

1. Auto-Immunity is the state in which the body's immune system fails to distinguish between self and non-self and reacts by formation of anti-bodies against one's own tissue antigens.
2. In other words, there is loss of tolerance to one's own tissues and hence it is contrary of immune tolerance.
3. Auto-Immunity is often caused by a lack of microbial development of a target body and as such the immune response acts against its own cells and tissues.
4. Auto-Immunity is very complex and there are many different auto-immune diseases; each affecting the body in vastly different ways.
5. Even patients with the same auto-immune disease may show different symptoms.

6. Generally (till date) these are life-long conditions, although medication and treatment can make quality of life better for the patient [1,2,4,5].

Figure 17: The tendency of immunity v/s tendency of auto-immunity.

AIED

It was first described by Dr. Brian McCabe in a landmark paper describing an auto- immune loss of hearing sensitivity inner ear that is usually progressive asymmetrical sensori-neural hearing loss. Audiometric test(s) reveal that the loss is typically ameliorated from steroids and immune-suppressants (till date).

Apart from inner ear inflammation associated with viral or bacterial labyrinthitis, it seemed ludicrous that the immune system could operate within the bony labyrinth. Researchers over the last few years have concluded that AIED is the result of anti-bodies or other immune cells that cause damage to the structures of the inner ear (mostly cochlear vasculitis).

Using the brain as a model, inner ear was initially viewed as an immunologically privileged site, separated from cellular and humoral immunity by a blood-labyrinthine barrier. Moreover, antigens introduced into the inner ear of a systemically immunized animal resulted in hearing loss and even profound deafness owing to a vigorous secondary immune response. The magnitude of these responses was dependent on an intact endolymphatic sac since ablation of the sac or even blockage of the endolymphatic duct reduced inner ear immune responses. Inner Ear can be the direct target of the immune response, but it can additionally be damaged by the deposition of circulating immune system complexes or by systemic immune mediated diseases.

Experiments have demonstrated that the inner ear although protected by systemic immunity, was damaged by bystander injury when cell- mediated immunity became involved e.g. systemic immunity can protect the inner ear from viral infection through circulating anti-viral anti-bodies. However, if there is a cellular response to viral inoculation of a naive animal, there is cochlear damage and hearing loss [1,4,25,26].

Aetiological factors

The route of entry of inflammatory cells into the inner ear following antigen or viral change of the inner ear appears predominantly to be via the spiral modular vein. During the inflammatory response, this vein takes on characteristics of an activated venule and expresses intracellular adhesion molecule-1 (ICAM-1) on the endothelial cell surface that facilitates the passage of circulating immune- competent cells into the scala tympani.

An uncontrolled attack against the inner ear antigens, resulting in both T-cell responses and auto- antibody development, has been proposed as the pathogenetic mechanism.

Many antigens in the inner ear and possibly in the endolymphatic sac have been recognized as possible AIED targets and among these Cochlin (an extracellular matrix protein), specifically present in the inner ear has been proposed as a possible Cochlear antigen involved in the pathogenetic mechanism of AIED: Anti- Cochlin antibodies have been detected in a small cohort of patients affected and may advocate a cochlear specific antibody response.

AIED apparently is a consequence of electrochemical disturbances, microthrombosis and immune cell deposition due to underlying pathophysiology.

It has two sub- types:

1. Primary AIED- only the inner ear is involved.
2. Secondary AIED- occurs in a context of systemic AIED.

The onset of immune-mediated sensori-neural hearing loss is still not a well understood process due to:

1. Lack of ideal animal model.
2. Unreliable data obtained from peripheral blood studies.
3. Difficulty in assessing the anatomic structures of inner ear.

After the activation of the immune response and the release of interleukins (IL-α), the auto-immune response is promoted and hence the activated circulating Leukocytes and Immunoglobulins can target, by chemotaxis, the inner ear in response to antigenic stimuli. The TNF is also considered a pro-inflammatory Cytokine promoting the auto-immune response.

The pathogenesis of AIED could be a consequence of:

1. Deposition of circulating immune complexes (responsible for type- III immune system response).
2. Vestibule-cochlear auto-antibodies (responsible for type- II immune system response, Cytotoxic antibody mediated injury).
3. Vasculitis.
4. Micro-thrombosis.
5. Electro-chemical Alterations (HSP-70/68kD, bHSP).

Antigen introduced into the inner ear of a systemically immunised animal resulted in hearing loss owing to a vigorous secondary immune response upto profound degree.

The route of entry of inflammatory cells into inner ear following antigen or viral challenge of the inner ear appears predominantly via spiral modular vein. During the inflammatory response, this vein takes the traits of an activated venule and expresses Inter Cellular Adhesion Molecule-1 (ICAM-1) on the endothelial cell surface that facilitates the passage of circulating immuno-competent cells into scala tympani upon reaching Inner ear. These cells divide and then release the inflammatory mediators, set the events in motion, leading to cellular proliferation and eventually osteogenesis that ultimately causes hearing loss upon reaching the Cochlea. After the single inoculation of Antigen, cells may continue to be stimulated, undergoing cell division for upto 6 weeks and Meiniers may accompany these end stage reactions. Lymphocyte Migration Assays using inner ear tissue as a target have been disappointing. More promising results could be obtained with Western Blotting because specific immune reactivity against inner ear antigens is often in cases with suspected AIED but results may vary.

Significantly more patients with suspected AIED show reactivity against a 68 kD antigen than do matched normal hearing or rheumatic controls. AIEDs have also been associated with reactivity against antigens of different molecular weights (especially 45 - 50 kD, 30 kD and 20 kD).

Immunization with specific proteins has also resulted in hearing loss based on the observation that Myelin protein P0 was associated with immunoreactivity against a 30kD inner ear protein in patients with AIED.

Animal models of systemic auto-immune disease, such as MRL-Fas Ipr mouse model of Systemic Lupus Erythematosus (SLE), display hearing loss. The 68 kD antigen has been associated with HSP70 and immuno-reactivity against the Bovine HSP70 (bHSP 70) has been found to be correlated with AIED. However, pre-absorption with bHSP 70 has been doesn't remove all the reactivity to the 68 kD inner ear antigen and immunization of animals with HSP 70 doesn't appear to produce hearing loss.

bHSP70	HSP70
Bovine serum albumin (BSA or fraction-V) is a serum albumin protein derived from cows. Its often used in lab experiments by altering pH, concentration, etc.	The 70kD HSP are a family of conserved ubiquitously expressed HSP. Proteins with similar structures exist in virtually all living organisms and are an important part of cells' machinery for protein folding and protecting cells from stress.

Circulating monoclonal antibodies against inner ear tissues also produce hearing loss. Moreover, immunization of animals with crude extracts of inner ear tissues results in hearing loss in 1/3rd of the population. Several investigators have reported that immunoreactivity to inner ear proteins with molecular weights in 42 - 45 kD range is also positively correlated with AIED, although with a lower level of specificity than 68 kD protein or HSP 70.

Matsouka., *et al*. immunized mice with purified Bovine P0 and observed approximately 10dB HL hearing loss and a monocellular infiltrate in the eight nerve within the Cochlear Modiolus. Experimental auto-immune Encephalomyelitis can be induced by immunization with the neuronal S-100ß Calcium binding protein and by passive transfer of T-cells sensitized to this antigen.

Gloddek., *et al*. found that passive transfer of S-100ß-reactive T-cells produced a 10dB HL of hearing loss in rats as well as cellular infiltrate into the perilymph. In a retrospective case series, Hirose., *et al*. evaluated the variety of assays for the systemic auto-immune disease, as well as a Western Blotting Assay against the bHSP-70, for their utility in predicting the responsiveness of rapidly progressive sensori-neural hearing loss to corticosteroids.

Positivity in the HSP 70 Blot Assay was the best predictor of corticosteroid responsiveness although maximum reported sensitivity was 40% only. A monoclonal antibody raised against Cochlear tissues of 68kD that specifically reacts with supporting cells in the Organ of Corti has been shown to produce high frequency hearing loss in mice carrying the hybridoma.

More recently, Nair., *et al*. infused this antibody into the Cochlear perilymph using an osmotic minipump, after 13 days an approximately 20dB hearing loss developed, associated with minor losses of hair cells. To explore the origin of Lymphocytes in the region of Endolymphatic sac and the reaction of T-cells to self-antigens in the inner ear, Iwai., *et al*. used a model of graft v/s host disease. T-cells from C57BL/6 mice injected into the systemic circulation of BALB/c mice infiltrated and proliferated in the perisaccular region surrounding the endolymphatic sac but not to other regions in the inner ear. These findings confirm the role of the endolymphatic sac region in mediating immunity in the inner ear as well as the communication of the normal sac with circulating Lymphocytes and also provide an additional foundation for autoimmunity as an etiology in disorders involving the sac (Menier's Disease).

The MRL-FasIpr mouse is used as a model of SLE owing to accumulation of the auto-reactive T-cells normally eliminated by the Fas-mediated apoptosis, it also displays a progressive H.L. Ruckenstein., *et al*. found that the most striking inner ear pathology in this model was observed in stria vascularis, with progressive hydropic degeneration of intermediate cells, consistent with the trial pathology observed in human systemic lupus erythematosus temporal bones. Ruckenstein and Hu observed the deposition of both complement-fixing and non-complement-fixing antibodies in the stria vascularis and to a lesser extent, to other structures also. All antibodies were bound to capillary walls and there were not associated with signs of inflammation.

The same group found that systemic treatment with Dexamethasone suppressed antibody deposition within the stria and other structures of the inner ear.

Due to relative rarity of this condition and its recent recognition, very few temporal bones with a diagnosis of AIED have been evaluated. In a study by Sone., *et al*. they studied 14 temporal bones from 7 individuals with Systemic Lupus Erythematosus (SLE) assess their inner ears and most consistent findings revealed the loss of hair cells and spiral ganglions (duration of condition and age varied widely). However unusual accretions were observed in stria vascularis in 6 out 14 temporal bones.

Animal models have been valuable adjuncts in the study of AIED since the antigen and immunisation history can be rigorously controlled and histopathology is routinely available. Initial studies using immunization of guinea pigs with bovine inner ear extracts resulted in the development of hearing loss and mild inflammatory changes in the inner ears of subset of animals. More recent findings confirmed these findings and indicated that the hearing losses induced by this procedure tend to be modest. Boumanet. al. found that immunization of animals with swine inner ear extracts produced modest declines in compound action potentials recorded from the guinea pigs 2 and 6 weeks after immunization but no changes in the Cochlear Microphonics were recorded. This suggests that the event responsible for hearing loss occurred at the level of inner ear hair cell and/or spiral ganglion neuron rather than at the level of outer hair cells. Hearing losses were associated with increased Western Blot reactivity to 68kD and other antigens.

Theories that propose a cause of AIED:

1. **Bystander damage:** Physical damage to the INNER EAR. leading to Cytokine release signaling auto- immune response. This may be a component Attack/Remission Cycle of the Meiniers Disease.
2. **Cross-reactions:** Accidental Damage to the INNER EAR. by antibodies or the T-cells recognizing the inner ear antigens similar to bacterial or viral antigens.

3. **Intolerance:** Immune system may not be aware of all antigens present in inner ear until physical damage releases some of these unfamiliar antigens as foreign body and mounts an immune response [16,24,28].

Clinical manifestations

It can be heterogeneous, but in 80% of the cases there's >/30dB HL bilateral asymmetrical sensori-neural hearing loss, the thresholds however may be fluctuating. Later period may be characterized by the rapidly progressive onset of hearing loss over the weeks or months, usually between 30 - 90 days. It has been reported that frequently only one ear is affected in the chronic stages.

Interestingly, AIED is the only condition involving sensori-neural hearing loss that responds to the medical treatments but withholding treatment for longer than three months may result in irreversible hearing loss and hence the need for Cochlear Implant may arise. In 25 - 50% of the cases, Tinnitus and Aural Fullness can also be present.

Particular attention has to be paid to the timing of sensori-neural hearing loss onset, in order to distinguish an autoimmune Cochleopathy from a sudden sensori-neural hearing loss or from Presbyacusis because in almost 50% of the cases Vestibular Asymmetry is seen.

In some cases, hearing loss profile shows a conductive component that's affected by Granulomatosis with Polyangiitis, Eustachian tube and/or middle ear mucosa whereas, in 30% cases, AIED is secondary to systemic lupus Erythematosus, Rheumatoid arthritis or Sjogren's syndrome, Wegener's Granulomatosis. [4,6,13,15].

Diagnosis

The diagnosis of AIED is still exigent since there is no universally accepted set of diagnostic criteria or diagnostic test for a condition that appears to have several independent aetiologies. In general, in all cases of idiopathic, rapidly progressive bilateral hearing loss, AIED should be suspected. However, there is no doubt that involvement of the other ear may occur months or even years after presentation of symptoms in the first ear. Hearing loss may be manifested as either diminished hearing acuity, decreased discrimination or both and may involve significant fluctuations over time. In bilateral Meniere's disease, with its triad of vestibular dysfunction, low tone fluctuating hearing loss and tinnitus AIED should also be suspected; especially when the second ear is involved within a short period of time.

Aside from an empiric trial with high dose corticosteroids showing improved inner ear function, Western Blot Assays are currently the most widely used category of diagnostic test. The initial assays used for this purpose were based on proteins extracted from bovine inner ear tissue, and inner ear extracts are still being used. Reactivity to an approximately 68kD antigen was detected in a significant proportion with AIED patients [5,14,48,49].

Classification of AIED

Over the past two decades since McCabe's published article on AIED, many patients have been diagnosed and treated for rapidly progressive SENSORI-NEURAL HEARING LOSS and may have had their hearing maintained or even improved with treatment. As a result of the growing experience with patients with corticosteroid sensitive hearing loss, a pattern has begun to emerge that warrants a classification scheme to sort out patients better as they present with such a broad category of inner ear dysfunction.

Although the classification scheme is intended specifically for that purpose, it is likely that over the next few years it will refined further.

Type 1: Organ (ear) specific

1. Rapidly progressive bilateral sensori-neural hearing loss.
2. All age ranges, although middle age is most common.
3. No other clinical evidence of systemic autoimmune disease.
4. Positive Otoblot (Western blot 68 kD or HSP 70).
5. Negative serologic studies (antinuclear antibody [ANA], erythrocyte sedimentation rate, rheumatoid factor (RF), C1q binding assay, etc).
6. Greater than 50% response rate to high-dose corticosteroids.

Type 2: Rapidly progressive bilateral sensori-neural hearing loss with systemic AIED

1. Rapidly progressive bilateral sensori-neural hearing loss.
2. Hearing loss often worse with flare of auto-immune condition.

3. Other autoimmune condition is present (SLE, ulcerative colitis, Polyarteritis nodosa, vasculitis, rheumatoid arthritis, Sjogren's syndrome).
4. Otoblot may be positive or negative.
5. Serologic studies will be positive in accordance with the illness (i.e. ANA-high titers, RF positive, circulating immune complexes).
6. Corticosteroid responsive and may be managed with targeted therapies for underlying illness.

Type 3: Immune mediated Meniere's disease

1. Bilateral, fluctuating sensori-neural hearing loss with vestibular symptoms that may predominate.
2. Subset of patients with delayed contralateral endolymphatic hydrops or recent instability of better-hearing ear in a patient with burned out Meniere's disease.
3. Otoblot positive 37 to 58%; may show presence of circulating immune complexes.
4. Corticosteroid responsive; may require long-term immunosuppression owing to relapses.

Type 4: Rapidly progressive bilateral sensorineural hearing loss with associated inflammatory disease (Chronic otitis media, lyme disease, otosyphilis, serum sickness)

1. Evidence of profound drop in hearing with longstanding chronic otitis media.
2. May show inflammation of the tympanic membrane and perforations.
3. Hearing loss progresses despite treatment of the infectious agent (treponemal or rickettsial).
4. Otoblot negative; serologic tests for the underlying disease may be positive; patient should be evaluated for granulomatous disease and vasculitis by biopsy if tissue is available.
5. Corticosteroid responsive and may require long-term immunosuppression.
6. Serum sickness has been reported after vaccinations, although anecdotal.

Type 5: Cogan's syndrome

1. Sudden onset of interstitial keratitis and severe vestibule-auditory dysfunction.
2. Otoblot negative for 68 kD but positive for 55 kD antigen.
3. Responds to high-dose corticosteroids, although becomes resistant over long term.

Type 6: Auto-immune inner ear disease-like

1. Young patients with idiopathic rapidly progressive bilateral sensori-neural hearing loss leading to deafness.
2. Severe ear pain, pressure and tinnitus.
3. Otoblot and all serology negative.
4. May have an unrelated, nonspecific inflammatory event that initiates ear disease.
5. Not responsive to immunosuppressive drugs, although they are tried [17,18].

Treatment

Once a diagnosis of AIED is established or considered highly presumptive, high-dose prednisone is the mainstay of treatment for this condition. Early institution of 60 mg of prednisone daily for a month is now widely used as short-term or lower-dose long-term therapy and has either been ineffective or fraught with the risk of relapse. Prednisone is then tapered slowly if a positive response to therapy is obtained. If during the taper hearing suddenly falls, reinstitution of high-dose prednisone is indicated. One sensitive predictor of imminent relapse can be the appearance of loud tinnitus in one or both ears. If patients show corticosteroid responsiveness but attempts at taper result in relapse, the addition of a cytotoxic drug should be considered. The most widely used of these agents are methotrexate (MTX) and cyclophosphamide (Cytoxan). The former has the advantage of being less toxic and has fewer long-term hematopoietic risks, such as the development of neoplasia. If

MTX is used, it should be given as an oral dose 7.5 to 20 mg weekly with folic acid. The patient should be monitored closely for toxicity with complete blood count, platelets, blood urea nitrogen, creatinine, liver function tests, and urinalysis. It should be noted that the prednisone-sparing effects of MTX may take 1 to 2 months to achieve; therefore, prednisone should be maintained until such effects are obtained. Also, if high-dose prednisone has not been effective in restoring hearing, it is unlikely that MTX will offer additional efficacy.

For patients with severe hearing losses, positive 68 kD Western blots, and non-responsiveness to prednisone or MTX therapy, consideration should be given to a trial of cyclophosphamide. At oral doses of 1 to 2 mg per day taken each morning with liberal amounts of fluid, the risk of hemorrhagic cystitis on the bladder can be minimized. Again, appropriate monitoring of peripheral blood counts is required. Cyclophosphamide should not be administered to children and the risk of permanent sterility should be outlined. If, on the other hand, no response to high dose prednisone is achieved, and the patient is 68 kD Western blot negative, it may be futile to continue potentially toxic drugs, with little evidence for AIED as the cause.

As this field continues to evolve, there are, however, no hard and fast rules, and a practitioner may be justified in trying cytotoxic drugs on an empiric basis because unrelenting progressive deafness is a serious handicap for a previously normal-hearing person.

Luetje recommended Plasmapheresis for difficult to manage patients and this can be a useful adjunct to the above-mentioned immunosuppressive drugs. At the time of writing, a multi-institutional clinical trial is under way to compare the efficacy of MTX and prednisone versus prednisone alone for the management of AIED. The results of this trial should help to delineate appropriate therapy for suspected AIED.

Parnes., *et al*. noted that local corticosteroids appear to be more effective in the treatment of other autoimmune disorders, such as corneal inflammation owing to Cogan's syndrome. They therefore investigated the pharmacokinetics of hydrocortisone, methylprednisolone and dexamethasone in perilymph and endolymph after oral, intravenous, or intratympanic administration. Dexamethasone was found to be largely excluded from the cochlea by the blood-labyrinthine barrier. Both methylprednisolone and hydrocortisone reached inner ear fluid after systemic administration, attenuated presumably by the blood-labyrinthine barrier. Much higher levels of all three drugs were observed in cochlear fluid after intratympanic administration, with rapid declines over a 6- to 24-hour period. Similar results were noted by Chandrasekhar., *et al*. Parnes., *et al*. also reported that repeated intratympanic administration of corticosteroids in a small series of patients with hearing loss of diverse origins was followed by improvement in some patients, but no control group was included. In contrast, Yang., *et al*. found that local immunosuppression had no effect on experimental immune mediated sensori-neural hearing loss in an animal model. It should be noted that local effects are not, of course, the only basis for the therapeutic efficacy of immunosuppressants.

By decreasing peripheral blood leukocytes, these agents reduce the population of cells that can be recruited to the inner ear to participate in immune and inflammatory damage. An experiment designed to prevent entry of cells into the cochlea using antibodies to ICAM-1 did show a reduced number of infiltrated inflammatory cells in the cochlea following antigen challenge.

Although the inflammation was not entirely prevented, such a strategy may be worth pursuing. Despite the greater accessibility of the eye to topical drugs than the inner ear, ophthalmologists would never consider local therapy in lieu of high dose corticosteroids for these disorders. Perhaps a lesson taken from their experience might lessen the enthusiasm that currently exists for treatment solely by local middle ear corticosteroid instillation [21,27,33].

Discussion

Debate continues as to whether AIED exists as a separate entity. Some authors prefer to refer to this condition as immune-mediated inner ear disease. Clearly, the evidence for specific autoimmunity is indirect. Hearing and vestibular problems that are diagnosed as autoimmune in origin are often responsive to corticosteroids. Although this suggests that the condition involves inflammation, one cannot infer the involvement of specific immunity.

The fact that inner ear disease is often present in systemic autoimmune disorders provides strong evidence that autoimmune processes can damage the labyrinth but does not speak to the issue of organ-specific disease. Animal models of hearing loss and/or vestibular dysfunction secondary to immunization with inner ear antigens provide stronger evidence of specific autoimmunity. AIED

is increasingly considered as a potential cause of Meniere's disease and as a less likely cause of sudden hearing loss.

Improved diagnostic tests are clearly required. No one test appears to be positive in more than 30 to 40% of patients who otherwise fit the criteria for autoimmune disease. One possible explanation for this is that rapidly progressive sensori-neural hearing loss has a number of different causes, including autoimmune, viral, genetic, developmental, vascular, and perhaps metabolic. Many of these cannot be separated by their presentation; therefore, it would not be unusual or unexpected for many of these patients to have negative antibody testing, and some who were not autoimmune might even improve with corticosteroids (e.g. viral).

Another possibility is that autoimmunity exists to a variety of inner ear antigens. Given the variety of autoimmune disorders that can affect the inner ear, the variety of antigens with which sera from patients with AIED will react, and the fact that immunization with a variety of proteins can lead to hearing loss in animal models, this would appear to be a strong possibility.

The usefulness of Western blotting for antibodies directed against the 68 kD or HSP 70 antigen as diagnostic assay seems clear, although there is little evidence to support an etiologic role for HSP 70. It is possible that HSP 70 shares one or more epitopes with an inner ear antigen, although reactivity to widely variable epitopes of HSP 70 argues against this. Alternatively, HSP 70 immunoreactivity may all be a well-correlated epiphenomenon, perhaps produced by immunization of self-proteins during inflammatory responses arising from other causes. Lastly, initial studies with serum tested by Western blotting were with the use of 68 kD inner ear tissue as the target antigen.

After the recognition that HSP 70 showed results similar to 68 kD by several investigators, a number of groups have adopted HSP 70 as the target for immunologic testing. In fact, this may be the wrong approach if HSP 70 merely shares epitopes with but is not the actual antigen in 68 kD inner ear immunoreactivity. Future studies will certainly improve our knowledge of the actual antigenic target(s) involved in AIED.

Despite uncertainty over aetiology and difficulties in diagnosis, this condition is frequently responsive to treatment with immunosuppressive drugs. Since there are few forms of sensori-neural hearing loss that can be treated other than symptomatically, AIED represents a unique opportunity to reverse sensori-neural hearing loss and vestibular disorders. For this reason alone, the diagnosis should be considered when symptoms are appropriate, and both clinical and basic research on this condition is warranted [14,21,23,38].

Effect of auto- immunity on hearing and vestibular health

A. Hearing health: Inner ear can be the direct target of the immune response, but it can additionally be damaged by the deposition of circulating immune system complexes or by systemic immune-mediated diseases. The Auto-Immune Inner Ear Disorders (AIED) was first defined by Dr. Brian McCabe in a landmark paper describing an autoimmune loss of hearing sensitivity, inner ear. usually progressive asymmetrical Sensori-Neural Hearing Loss. Researches, over the last few years, have concluded that AIED is the result of antibodies or other immune cells that cause damage to the structures of the inner ear (mostly Cochlear Vasculitis). AIED apparently is a consequence of electrochemical disturbances, microthrombosis, immune cell deposition due to underlying pathophysiology. There are 2 sub-types of AIED:

   a. **Primary AIED:** Only the inner ear is involved

   b. **Secondary AIED:** Occurs as a context of systemic AIED. Its prevalent in 15 - 20% of case(s) [1,8,15].

B. Vestibular health: The human vestibular system estimates the body position and motion. Motion inputs to the vestibular system include the inner ear signals, as well as positional sensations, visual signals and intended movements. Balance information to the brain is sent by the eyes, muscles and joints and most importantly the ears. There are a total of 5 balance sensors in the ear; 3 of them are responsible for checking rotational motion and are called the semi-circular canals. 2 of them check the linear motions inner ear. going up-down and front-back. They are the Otolith organs called Saccule and Utricle. When a patient suffers from imbalance, there may be a problem with one or more of these sensors. This therefore requires full assessment of all sensors of balance to find out the origin and source of problem [2-4,40].

If the vestibular system gets affected (since the semi-circular canals are located in middle ear so any condition involving middle

ear might upto some extent affect the body balance) by the auto-immune reactions it will result in but is not limited to:

A. Dizziness

B. Vertigo

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