

## Otorhinolaryngological Manifestations of Skin Disease

Ümit Türsen,<sup>1\*</sup> MD, Belma Türsen,<sup>2</sup> MD

Address: <sup>1</sup>Mersin University, School of Medicine, Department of Dermatology and <sup>2</sup>Mersin State Hospital, Department of Dermatology, Mersin, Turkey

E-mail: utursen@mersin.edu.tr

\* Corresponding Author: Dr. Ümit Türsen, Mersin University, School of Medicine, Department of Dermatology, Mersin, Turkey

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### Abstract

**Background:** Many diseases present with both otorhinolaryngological and dermatological manifestations. Each case is followed by a discussion and a brief review of the characteristic cutaneous and otorhinolaryngological findings. The intent is to demonstrate classic dermatologic manifestations of diseases seen by otorhinolaryngologists.

### Introduction

Skin diseases are associated with a variety of problems in the head and neck region. This manuscript reviews the common otologic, nasal and paranasal sinus, oral and pharyngeal, and neck manifestations of skin diseases and discusses the evaluation and management of these problems. Although the majority of these problems can be initially evaluated and treated by the dermatologists, given the anatomy of the region and the need for a complete head and neck examination for many of these problems, all but the simplest cases should involve consultation with an ear-nose-throat specialist. Hearing loss, or deafness, can be present at birth, or become evident later in life in some skin disease. The distinction between acquired and congenital deafness specifies only the time that the deafness appears. It does not specify whether the cause of the deafness is genetic. Acquired deafness may or may not be genetic. For example, it may be a manifestation of a delayed-onset form of genetic deafness. Alternatively,

acquired deafness may be due to damage to the ear due to noise or from other conditions. Congenital deafness similarly may or may not be genetic. For example, it may be associated with a white forelock, and be caused by a genetic disease called Waardenburg syndrome. In fact, more than half of congenital hearing loss is inherited. Alternatively, congenital deafness may be due to a condition or infection to which the mother was exposed during pregnancy, such as the rubella virus. Hearing loss can also be classified based on which portions of the hearing system are affected. When the nervous system is affected, it is referred to as sensorineural hearing loss. When the portions of the ear that are responsible for transmitting the sound to the nerves are affected, it is referred to as conductive hearing loss. Conditions affecting the cochlea, eighth cranial nerve, spinal cord, or brain cause sensorineural hearing loss. Examples include; nerve injury from syphilis, nerve tumors and drug toxicity. Conditions that affect the ear canal, eardrum, and middle ear lead to conductive hearing

loss. Examples of conductive hearing loss include ear wax blocking the ear canal in psoriasis or seborreic dermatitis. Symptoms of hearing loss include mild loss of high frequency hearing, hearing loss associated with ringing or noises, and complete deafness. Symptoms may develop gradually over time with many causes of hearing loss. People who are experiencing hearing loss may refrain from taking part in conversations, may turn the volume up high on the radio or TV, and may frequently ask others to repeat what they have said. The treatment of hearing loss depends on its cause. For example, ear wax can be removed, ear infection can be treated with medications, diseases that cause inflammation of the ear can be treated with medication, medications that are toxic to the ear can be avoided or occasionally surgical procedures are necessary. Sensorineural causes are from damage to the hair cells or nerves that sense sound waves. Vascular diseases, include sickle cell disease, diabetes, leukemia, polycythemia, vasculitis and diseases in which excessive blood clotting occurs. Acoustic neuroma is a tumor in the auditory nerve. Usually associated with ringing in the ears. Infections such as mumps, measles, influenza, herpes simplex, herpes zoster, mononucleosis, syphilis, meningitis can lead to sensorineural hearing loss. The causes of most otolaryngologic manifestations of skin disease fall into the following categories: infections, neoplasms, genetic syndromes, medications, pigmentary disorders, allergic and autoimmune disease [1, 2, 3, 4, 5].

#### **A- Autoimmune Disease**

Both allergy and traditional autoimmune disease such as Ankylosing spondylitis, Behçet's, Systemic Lupus Erythematosus (SLE), Sjogren's syndrome (dry eye syndrome), Cogan's disease, ulcerative colitis, Wegener's granulomatosis, relapsing polychondritis, rheumatoid arthritis, and scleroderma can cause or be associated with autoimmune inner ear disease. When a virus attacks, the immune system defends the body. When the immune system malfunctions, its defense capabilities sometimes mistake the body's own cells for invading viruses or germs and attack them, which is referred to as autoimmunity. The

immune system can attack the whole body or just certain systems, including the ear. When the ear is itself attacked, this is known as autoimmune inner ear disease. The progression of damage and functional loss caused by autoimmune inner ear disease can be rapid [2].

#### **1. Scleroderma**

Scleroderma can affect every part of the body, including the ears. Many autoimmune diseases can cause autoimmune ear disease. Treatment goals in autoimmune inner ear disease include improving speech thresholds to levels treatable with hearing aids in severely affected patients and recovery of hearing to near normal levels in those with mild to moderate losses. If caught early, and with aggressive medical management, hearing stabilization and possible improvement are feasible. Hearing loss in diffuse cutaneous systemic scleroderma. Patients with diffuse scleroderma have a high prevalence of sensorineural audiometric hearing impairment and otological complaints, suggesting that the cochlea is an additional target organ in this disease. Ear involvement is frequent in systemic sclerosis and should be taken into consideration during diagnostic and therapeutic procedures. For subjects affected by scleroderma, the restoration of synchronous neural discharge could be achieved by electrical stimulation through cochlear implant [6, 7].

#### **2. Ménière's Disease**

Meniere's disease is an abnormality of the inner ear causing a host of symptoms, including vertigo or severe dizziness, tinnitus or a roaring sound in the ears, fluctuating hearing loss, and the sensation of pressure or pain in the affected ear. The disorder usually affects only one ear and is a common cause of hearing loss. Proposed theories of causation include viral infections and immune system-mediated mechanisms. Despite some limitations, Meniere's Disease displays an elevated prevalence of systemic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis [8].

### 3. Inflammatory Bowel Diseases

It was reported histopathological and immunohistochemical findings of the inner ear of a patient with a granulomatous inner ear disease suffering from Crohn's disease that was nonresponsive to treatment and who underwent surgery for bilateral cochlear implants. Inflammatory bowel disease is becoming increasingly frequent in children of all ages. In addition to the usual gastrointestinal stigmata of weight loss, anaemia, and rectal bleeding, children may exhibit prominent extra-intestinal manifestations such as joint symptoms, skin signs and some other autoimmune manifestations. Authors presented a 15-year-old girl with ulcerative colitis in whom pyoderma gangrenosum and acute sensorineural hearing loss developed. Although pyoderma gangrenosum is well described with inflammatory bowel disease, sensorineural hearing loss is very rare [9, 10].

### 4. Behçet's Disease

Behçet's disease causes canker sores or ulcers in the mouth and on the genitals and inflammation in parts of the eye. In some people, the disease also results in arthritis, skin problems, and inflammation of the digestive tract, brain, and spinal cord. Behçet's disease is common in the Middle East, Asia, and Japan; it is rare in the United States. In Middle Eastern and Asian countries, the disorder affects more men than women. In the United States, the opposite is true. Behçet's disease tends to develop in people in their twenties or thirties, but people of all ages can develop it. The exact cause of Behçet's disease is unknown. Most symptoms of the disorder are caused by inflammation of the blood vessels. Doctors think that an autoinflammatory reaction may cause the blood vessels to become inflamed, but they do not know what triggers this reaction. Corticosteroids and immunosuppressive drugs are commonly used to treat the disease. It is a chronic recurrent inflammatory disorder involving the small and large vessels. Typical loci of manifestations are the mucous membranes, skin and eyes, as well as the joints and central nervous system. Other organs are not commonly involved. Some patients could have sudden hearing or tinnitus. Careful examination re-

vealed vestibular involvement in the first patient and retrocochlear involvement in the second. Inner ear involvement is an uncommon manifestation of Behçet's disease. In case of relevant signs or history, such as hearing disturbance, tinnitus and/or vertigo, patients should be examined for inner ear involvement [5, 11].

### 5. Vasculitis

Hearing can be transiently decreased in patients with granulomatosis with polyangiitis with acute otitis, because of the presence of liquid in the inner ear, which will regress under appropriate treatment. However, when the inner ear damage is severe, because of prolonged or multiple recurrences of otitis, and/or when the auditory nerve are involved by inflammation or compression, the hearing loss can be permanent. The symptoms of vasculitis depend on the particular blood vessels that are involved by the inflammatory process. Different types of vasculitis involve blood vessels in characteristic locations throughout the body [12, 13, 14].

**Giant Cell Arteritis** typically involves the medium- to large-sized blood vessels supplying the head and neck, but rarely involves the blood vessels of the kidneys [12].

**Wegener's Granulomatosis** frequently involves the kidneys, very often the lungs, and almost always the upper respiratory tract, but rarely blood vessels to the brain. Chronic sinus congestion and "infections" that persist for longer than they should; hearing loss; inflammation of the nasal septum, sometimes resulting in a perforation or collapse of the bridge of the nose. Patients could presented with otalgia and otitis media or hearing loss, fulminant sinusitis, arthralgias, and even corneal ulcers. Sometimes, the patients had "typical" rhinitis and nasal congestion. Biopsy of these sites frequently demonstrated necrotizing vasculitis. In the teenager and young adult, with an unusual constellation of symptoms of the head and neck and accompanying systemic problems, a diagnosis of Wegener's granulomatosis should be seriously considered [14, 15].

**Cogan syndrome**, a rare vasculitis characterized by systemic, ocular, and audio-vestibular symptoms. In *Cogan* syndrome, vestibular symptoms including vertigo, vomiting, and dizziness and auditory involvement including sensorineural hearing loss, tinnitus, and deafness may occur. Audiovestibular and ocular involvement have a major impact on prognosis in children with *Cogan* syndrome. *Wegener* granulomatosis is an immune-mediated, systemic vasculitis with unknown etiology that can be seen in almost any anatomical site. Positivity for antineutrophil cytoplasmic antigens, which is a serological marker, and presence of granulomatous vasculitis in histopathologic specimens from the lesions are accepted as diagnostic. *Wegener* granulomatosis could be present symptoms and signs are related to otologic and meningeal involvement [13].

### 6. Immune Thrombocytopenic Purpura (ITP)

Otolaryngological manifestations of 90 patients with immune thrombocytopenia purpura have been studied. Among the sick children, epistaxis was the most common complaint, followed by gum, buccal, conjunctive, tongue, lips, eyelids, facial and throat bleeding, in this order. Severity and recurrence were correlated with the sick children's condition: the presence or absence of local trauma and infection, blood platelet level and capillary fragility, especially in acute I.T.P. Other conditions included: hearing loss, vertigo, or dizziness, tinnitus, facial paralysis and so on. They concluded immune responses may be important in the etiopathogenesis of these non-hemorrhagic abnormalities, and should not be ignored in treating the problems as result of I.T.P [16].

### 7. Pemphigus Vulgaris (PV)

It is a life-threatening autoimmune bullous disease, mediated by autoantibodies directed against antigens on the keratinocyte cell surface of stratified squamous epithelia. The frequency of ear, nose, and throat (ENT) involvement in PV is not clearly identified. In a study, authors evaluated the ENT involvement in new patients with PV examined by ENT endoscopy before and after

treatment. In ENT examination of patients before the treatment, 11 (26.8%) patients showed ear, 15 (36.6%) nasal, 37 (90.3%) oral, 25 (61%) pharyngeal, and 24 (58.5%) laryngeal involvement. Thirty patients underwent the posttreatment ENT examination. They founded ear signs in 2 (6.7%), nasal involvement in 1 (3.3%), oral signs in 4 (13.3%), pharyngeal manifestations in 6 (20%), and laryngeal signs in 3 (10%) patients after treatment. The treatment was significantly effective in the improvement of mucosal lesion in different sites ( $P < .01$ ). ENT evaluation might be worthwhile to evaluate the disease extension in patients with PV more definitely and exclude other potential etiologies in recalcitrant patients [17, 18].

## B- Inflammatory Skin Disease

When inflammation is complicated by bacteria and/or candida infections, it can cause the ears to be dry, itchy and flaky. A good prescription ointment for this is called Kenacomb Ointment. The patients can use a Q-tip to carefully wipe a very thin layer over the inner ear. It really does stop the itching. Kenacomb is a corticosteroid, anti-inflammatory, antipruritic, antibacterial and anti fungal ointment and is indicated for use only for: Corticosteroid-responsive inflammatory or pruritic dermatoses caused, threatened or complicated by infection due to bacteria and/or candida [12].

### 1. Sarcoidosis

This multisystem chronic inflammatory condition is characterized by the formation of non-caseating epithelioid granulomata at various sites in the body. It has a predilection for the lungs and thoracic cavity, but there are protean manifestations that may catch out even the most experienced physicians. Despite having been described since the mid-nineteenth century or so, the underlying aetiology remains uncertain. It appears likely that a genetic susceptibility is combined with a triggering infection but, despite several candidate genes and micro-organisms being suggested, there is no definitive evidence in favour of particular ones, as yet. There is



considerable variability of the disease in different people and explaining this may help to develop new approaches to treatment. It largely affects patients in their mid-twenties to mid-forties but cases do appear infrequently in younger and older patients. After the thorax, the skin and eyes are most commonly affected, followed by the liver, heart and nervous system. This is highly variable depending on ethnicity, duration of illness, pattern and degree of inflammatory organ involvement. The dermatologists should check for lymphadenopathy, salivary gland swelling, tonsillar enlargement/inflammation and patency/abnormality of nasal passages if there are any relevant symptoms. In patients, fever and night sweats, malaise, fatigue, weight loss and Heerfordt's syndrome characterised by inflammation of submaxillary/parotid glands with uveitis and facial nerve palsy may accompany constitutional presentation. In neurosarcoidosis, infiltrative nerve lesions can affect any part of the central or peripheral nervous system, leading to a huge variety of neurological disease. Bell's palsy and lymphocytic meningitis are common manifestations of neurological involvement but diabetes insipidus is also seen. The following symptoms are encountered relatively commonly as a result of neurological involvement: Facial numbness, dysphagia, hoarseness, headache, visual field defects, polydipsia, hearing impairment, lesions of cranial nerves VII, VIII, IX and X, bitemporal hemianopia due to optic chiasmal involvement, seizures, stroke/transient ischaemic attack, peripheral neuropathic lesions. Other areas including upper respiratory tract (causing nosebleeds, rhinitis, nasal obstruction/masses or tonsillar involvement) and salivary glands (causing facial swelling and pain and other symptoms of parotitis) rarely involved. Ear, nose and throat complications of sarcoidosis including salivary gland dysfunction, nosebleeds and nasal obstruction are usually treated with high-dose oral steroids as first-line therapy. Refractive cases of otorhinolaryngological disturbance or aggressive otorhinolaryngological granulomata formation may be given adjunctive therapy

with immunosuppressants such as azathioprine or ciclosporin [19].

## **2. Relapsing Polychondritis (RP)**

This is a rare autoimmune disorder of unknown etiology. The disease is characterized by episodic inflammation and destruction of cartilaginous and connective tissue structures, including the ear, eye, nose, larynx, trachea, bronchi, joints, skin, heart valves, and aorta. As the symptoms of RP are diverse and complex, it is easily misdiagnosed. In a study, 15 patients with RP were analyzed retrospectively and the relevant literature reviewed. The number of patients presenting with auricular chondritis was 13, while two presented with poly-arthritis. Among them, the treatment of 2 RP patients with respiratory tract involvement failed and 1 patient died. Eleven patients with RP (73%) were initially misdiagnosed. RP involves cartilage and connective tissue. The prognosis for patients with respiratory tract involvement is poor. RP causes episodic and progressive inflammation of cartilage throughout the body and is associated with a variety of clinical manifestations. Early diagnosis of RP depends on a thorough understanding of its clinical features [20].

## **C- Genetic Syndromes**

### **1. Neurofibromatosis:**

Neurofibromatosis is a disease that affects the development and growth of nerve cell tissues. It causes tumors to grow on nerves and can affect many systems in the body including the skin, skeleton, and brain. The tumors, called neurofibromas, are usually benign (noncancerous) and grow on nerves within the body, as well as on and under the skin. Neurofibromatosis can cause skin changes, bone deformities, and other problems. In many cases, symptoms are present at birth or develop during childhood. Some people have symptoms that are mild or not noticeable at all. In other people, neurofibromatosis causes significant disability. There is no cure for neurofibromatosis. Many symptoms, however, can be treated and managed. Children with more

severe symptoms will naturally require more medical attention than children who have mild symptoms. In many cases, neurofibromatosis symptoms worsen as a patient ages. Neurofibromatosis Type 1 is the more common form of the disease, occurring in 1 in 3,000 to 4,000 births. Also known as von Recklinghausen disease, NF1 mostly affects nerves of the outer parts of the body. Neurofibromatosis Type 2 is less common, occurring in 1 in 25,000 to 40,000 births. Also known as bilateral acoustic neurofibromatosis, NF2 mostly affects the central nervous system, causing tumors of the brain and spinal cord. Hearing loss that begins in the teens or early twenties is often the first symptom of NF2. People with NF2 may develop.

**Auditory nerve tumors:** Most people affected by NF2 develop tumors on the nerves needed for hearing. Although the tumors are usually benign (noncancerous), they often lead to progressive hearing loss as they grow. Acoustic neuroma (also called a vestibular schwannoma) is a serious but nonmalignant tumor that develops on the sheath of inner ear's vestibulo-cochlear nerve, which transmits both balance and sound information to brain. As an acoustic neuroma grows, it compresses the vestibulo-cochlear nerve, usually causing hearing loss, tinnitus, and dizziness or loss of balance.

**Other complications:** Affected people may also have ringing in the ear(s), headaches, facial pain/numbness, and trouble with their balance.

**Neurofibromatosis 2 (NF2)** is much less common than NF1. Signs and symptoms of NF2 usually result from the development of vestibular schwannomas in both ears. These benign tumors grow on the nerve that carries sound and balance information from the inner ear to the brain (the eighth cranial nerve). Resulting signs and symptoms generally appear in the late teen and early adult years and may include gradual hearing loss, ringing in the ears, poor balance. Schwannomatosis is a rare form of neurofibromatosis only recently recognized. It rarely affects people before their 20s or 30s. Schwannomatosis causes painful tumors called schwannomas to develop on cranial,

spinal and peripheral nerves, but not on the nerve that carries sound and balance information from the inner ear to the brain. Because tumors don't grow on this nerve, schwannomatosis doesn't cause hearing loss, making it different from NF2. As with NF2, though, schwannomatosis doesn't cause cognitive impairment. Schwannomatosis mainly causes chronic pain, which can occur anywhere in your body. Approximately half of the cases of neurofibromatosis are inherited. The other half are caused by a spontaneous mutation of the gene. Children with neurofibromatosis often need regular medical evaluations to measure growth and blood pressure, and to examine skin, bones, the nervous system, vision, and hearing. Adults with neurofibromatosis often need yearly evaluations of the nervous system and hearing [21].

## 2. Syndromes with Connexins Mutations

The GJB2 gene is located on chromosome 13q12 and it encodes the connexin 26, a transmembrane protein involved in cell-cell attachment of almost all tissues. GJB2 mutations cause autosomal recessive (DFNB1) and sometimes dominant (DFNA3) nonsyndromic sensorineural hearing loss. Moreover, it has been demonstrated that connexins are involved in regulation of growth and differentiation of epidermis and, in fact, GJB2 mutations have also been identified in syndromic disorders with hearing loss associated with various skin disease phenotypes. GJB2 mutations associated with skin disease are, in general, transmitted with a dominant inheritance pattern. Nonsyndromic deafness is caused prevalently by a loss-of-function, while literature evidences suggest for syndromic deafness a mechanism based on gain-of-function. The spectrum of skin manifestations associated with some mutations seems to have a very high phenotypic variability. Several connexin are expressed in the cochlea, but the most abundant expression was found for Cx26 and Cx30 proteins which co-localize and can form heteromeric channels. They are expressed in nonsensory epithelial cells among which hair cells are dispersed and connective tissue cells at more distal locations to the hair cells. Despite se-

veral studies their function in inner ear is poorly understood. In these cells it has been supposed that gap junctions are important for maintaining the endocochlear potential being involved in recycling endolymphatic K<sup>+</sup> ions from the sensory hair cells back to the endolymph. GJB2 mutations, as well as other connexins, have been reported as causative for several syndromic forms of hearing loss associated to skin problems. Below is reported a brief description for each syndrome [22].

#### **a. Keratitis-Ichthyosis-Deafness (KID) Syndrome**

KID syndrome is a rare congenital ectodermal disorder, characterized by the presence of skin lesions, mild to profound sensorineural hearing loss, and vascularizing keratitis that can result in progressive decline of visual acuity and may eventually lead to blindness. The skin lesions, described as erythro-keratoderma are not restricted to particular regions of the body and show marked ichthyosis with increased susceptibility to mucocutaneous infection sometimes fatal in the neonatal period [23].

#### **b. Hystrix-Like Ichthyosis Deafness Syndrome (HID)**

HID deafness syndrome is similar to KID syndrome and displays all of the common features of KID. Symptoms are bilateral hearing loss and spiky hyperkeratotic masses which cover the whole body though the palms and soles are less badly affected. It can be differentiated from KID syndrome which also has symptoms of deafness and ichthyosis by the different distribution of hyperkeratosis. Actually, it is supported the idea that these two syndromes might represent a single form of syndromic deafness with a heterogeneous phenotype. Combined with the similarities between Vohwinkel syndrome (VS), Bart-Pumphrey syndrome (BPS) and palmoplantar keratoderma (PPK), the emerging view is that there are two broad types of skin disorder

associated with syndromic deafness: the VS-BPS-PPK group and the KID-HID group [24].

#### **c. Palmoplantar Keratoderma with Deafness Syndrome**

Palmoplantar keratoderma is another syndromic complication of deafness. Hereditary palmoplantar keratodermas (PPK) comprise a clinically and genetically heterogeneous group of genodermatoses, which share impaired epidermal differentiation resulting in prominent palmo-plantar hyperkeratosis. Classically, keratodermas have been separated according to their clinical appearance into diffuse, focal, and as a feature of ectodermal dysplasias and many other syndromes [25].

#### **d. Vohwinkel Syndrome**

Vohwinkel syndrome is another skin disease associated with SNHL. The skin problem is characterized by disturbed epidermal differentiation manifested by hyperkeratosis especially on the palms and soles (keratoderma), which, in the case of VS, often becomes mutilating with starfish-shaped proximal extensions and hyperkeratotic bands around the fingers, so-called pseudoainhum, sometimes leading to auto-amputation [26].

#### **e. Bart-Pumphrey Syndrome**

Bart-Pumphrey syndrome, is a rare autosomal dominant disorder characterized by congenital SNHL, palmoplantar hyperkeratosis, knuckle pads, and leukonychia (nail thickening and crumbling) [27].

### **3. Branchiooculofacial Syndrome**

The branchiooculofacial syndrome (BOFS) is characterized by: branchial skin defects that range from barely perceptible thin skin or hair patch to erythematous "hemangiomatous" lesions to large weeping erosions; ocular anomalies that can include microphthalmia, anophthalmia, coloboma, and nasolacrimal duct stenosis/atresia; and facial anomalies that can include ocular hypertelorism or

telecanthus, broad nasal tip, upslanted palpebral fissures, cleft lip or prominent philtral pillars that give the appearance of a repaired cleft lip with or without cleft palate, upper lip pits and lower facial weakness. Malformed and prominent pinnae and hearing loss from inner ear and/or petrous bone anomalies are common. Intellect is usually normal. The diagnosis is based on clinical findings. TFAP2A is the only gene in which mutations are currently known to cause BOFS. In general, children with BOFS should be managed by a multispecialty team including, for example, craniofacial specialists, plastic surgeons, otolaryngologists, and speech therapists. Small, linear or superficial branchial skin defects may heal spontaneously; however, some require surgical intervention. Anophthalmia or severe microphthalmia may require a conformer (a structure, usually plastic, inserted into the eye socket to encourage its growth); nasolacrimal duct stenosis or atresia often requires surgery. It is recommended that cleft lip be repaired by an experienced pediatric plastic surgeon. Lesser forms of cleft lip ("pseudocleft") may need surgical correction. Surveillance: Monitor for changes related to the major findings over time. BOFS is inherited in an autosomal dominant manner. De novo mutations are observed in 50%-60% of affected individuals. Each child of an individual with BOFS has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation of an affected family member has been identified [28].

#### **4. Congenital Lamellar Ichthyosis**

There is a case of osseointegrated hearing device placement in a child with conductive hearing loss related to manifestations of congenital lamellar ichthyosis. A 5-year-old female patient with congenital lamellar ichthyosis resulting in conductive hearing loss because of bilateral external auditory canal stenosis and tympanic membrane blunting. Unilateral osseointegrated hearing device placement using a traditional skin flap technique. Osseointegrated hearing device placement may be a viable option in patients

with congenital lamellar ichthyosis despite the skin-related comorbidities known to be associated with this disease condition [29].

#### **5. H Syndrome (OMIM 612391)**

It is a recently described autosomal recessive genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin and systemic manifestations including hepatosplenomegaly, cardiac anomalies, hearing loss, hypogonadism, low height, hypertriglyceridemia, hallux valgus, and flexion contractures. H syndrome results from mutations in the SLC29A3 gene, which encodes the human equilibrative nucleoside transporter hENT3. The cutaneous histopathology is characterized by a striking mononuclear cell infiltrate in the dermis consisting of CD68+ monocyte-derived cells and CD34+ and factor XIIIa+ dendrocytes. We describe a case of H syndrome in which the infiltrating mononuclear cells were CD68+, CD163+, S-100+, and CD1a-, thus simulating the immunophenotype observed in Rosai-Dorfman disease (RDD). The immunostaining for CD21, fascin, and CD34 were negative, and there were also many factor XIIIa+ dendrocytes interspersed within the dense mononuclear cell infiltrate. Recent findings of biallelic mutations in SLC29A3 in 2 families reported to have familial RDD and in a kindred with Faisalabad histiocytosis (OMIM 602782), which is an autosomal inherited form of histiocytosis with similarities to RDD, may explain the RDD-like immunophenotype in our H syndrome case [30].

#### **6. Xeroderma pigmentosum (XP)**

This syndrome is characterized by sun sensitivity (severe sunburn with blistering, persistent erythema on minimal sun exposure, marked freckle-like pigmentation of the face before age two years), ocular involvement (photophobia, keratitis, atrophy of the skin of the lids), and a greatly increased risk of cutaneous neoplasms (basal cell carcinoma, squamous cell carcinoma, melanoma). Approximately 25% of affected individuals have neurologic manifestations including acquired microcephaly, diminished or absent



deep tendon stretch reflexes, progressive sensorineural hearing loss, and progressive cognitive impairment. The most common causes of death are skin cancer, neurologic degeneration, and internal cancer [31].

### **7. Muckle-Wells Syndrome (MWS)**

It is an inherited autoinflammatory disease resulting in excessive interleukin-1 release. It is unknown whether demographic, clinical, or laboratory characteristics at the time of diagnosis may identify patients who are at high risk for severe disease activity. The most frequent organ manifestations were musculoskeletal symptoms and eye and skin disorders. Renal disease and hearing loss were seen in >50% of the patients [32].

### **8. Cockayne Syndrome**

It spans a phenotypic spectrum that includes: CS type I, the "classic" or "moderate" form; CS type II, a more severe form with symptoms present at birth; this form overlaps with cerebrooculofacioskeletal syndrome (COFS) or Pena-Shokeir syndrome type II; CS type III, a milder form; Xeroderma pigmentosum-Cockayne syndrome (XP-CS). CS type I (moderate CS) is characterized by normal prenatal growth with the onset of growth and developmental abnormalities in the first two years. By the time the disease has become fully manifest, height, weight, and head circumference are far below the fifth percentile. Progressive impairment of vision, hearing, and central and peripheral nervous system function leads to severe disability; death typically occurs in the first or second decade. CS type II (severe CS or early-onset CS) is characterized by growth failure at birth, with little or no postnatal neurologic development. Congenital cataracts or other structural anomalies of the eye may be present. Affected children have early postnatal contractures of the spine (kyphosis, scoliosis) and joints. Death usually occurs by age seven years. CS type III (mild CS or late-onset CS) is characterized by essentially normal growth and cognitive development or by late onset. Xeroderma pigmentosum-Cockayne syndrome (XP-CS) includes facial

freckling and early skin cancers typical of XP and some features typical of CS, including intellectual disability, spasticity, short stature, and hypogonadism. XP-CS does not include skeletal involvement, the facial phenotype of CS, or CNS dysmyelination and calcifications. Classic Cockayne syndrome (CS) is diagnosed by clinical findings including postnatal growth failure and progressive neurologic dysfunction along with other minor criteria. Molecular genetic testing or a specific DNA repair assay on fibroblasts can confirm the diagnosis. The two genes in which mutations are known to cause Cockayne syndrome are ERCC6 (65% of individuals) and ERCC8 (35% of individuals). Criteria required for the diagnosis include poor growth and neurologic abnormality; other very common manifestations include sensorineural hearing loss, cataracts, pigmentary retinopathy, cutaneous photosensitivity, and dental caries [33, 34].

### **9. Kallmann Syndrome (KS)**

It is characterized by the association of isolated GnRH deficiency (IGD) and anosmia (absent sense of smell). Infant boys often have micropenis and cryptorchidism. Adolescents and adults with IGD have clinical evidence of hypogonadism and incomplete sexual maturation on physical examination. Adult males with KS tend to have pre-pubertal testicular volume, absence of secondary sexual features (e.g., facial and axillary hair growth, deepening of the voice), decreased muscle mass, decreased bone densities, diminished libido, erectile dysfunction, and infertility. Adult females have little or no breast development and primary amenorrhea. Body habitus is usually eunuchoidal with arm span exceeding height by 5 cm or more. Although skeletal maturation is delayed, the rate of linear growth is usually normal (except for the absence of a distinct pubertal growth spurt). Individuals with anosmia may or may not be aware of their olfactory deficiency. Additional non-reproductive findings can include synkinesia of the digits, unilateral renal agenesis, sensorineural hearing loss, cleft lip and/or palate, agenesis of one or

more teeth, brachydactyly, syndactyly and agenesis of the corpus callosum [35].

### **10. Biotinidase Deficiency**

If untreated, young children with profound biotinidase deficiency usually exhibit neurologic abnormalities including seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous abnormalities including alopecia, skin rash and candidiasis. Older children and adolescents with profound biotinidase deficiency often exhibit motor limb weakness, spastic paresis, and decreased visual acuity. Once vision problems, hearing loss, and developmental delay occur, they are usually irreversible, even with biotin therapy. Individuals with partial biotinidase deficiency may have hypotonia, skin rash, and hair loss, particularly during times of stress [36].

### **11. MELAS Syndrome**

MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) is a multisystem disorder with onset typically in childhood. Early psychomotor development is usually normal, but short stature is common. Onset of symptoms is frequently between the ages of two and ten years. The most common initial symptoms are generalized tonic-clonic seizures, recurrent headaches, anorexia, and recurrent vomiting. Exercise intolerance or proximal limb weakness can be the initial manifestation. Seizures are often associated with stroke-like episodes of transient hemiparesis or cortical blindness. These stroke-like episodes may be associated with altered consciousness and may be recurrent. The cumulative residual effects of the stroke-like episodes gradually impair motor abilities, vision, and mentation, often by adolescence or young. The MELAS syndrome belongs to the category of mitochondrial disorders. The most common molecular etiology of the syndrome is a mutation A to G transition at base pair 3243 in the mitochondrial genome. The phenotype is varied and depends on the proportion of DNA mutated and which organ on aerobic metabolism suffers most. Neurosensory hearing loss, renal disease,

cardiomyopathy, diabetes mellitus, lactic acidosis and stroke-like episodes can be seen in MELAS syndrome. The skin manifestations of patients with MELAS syndrome are scaly, pruritic, diffuse erythema, reticular pigmentation, moderate hypertrichosis, seborrheic eczema, atopy and vitiligo [37].

### **12. Hutchinson-Gilford Progeria Syndrome (HGPS, Progeria)**

It is characterized by clinical features that develop in childhood and resemble some features of accelerated aging. Although signs and symptoms vary in age of onset and severity, they are remarkably consistent overall. Children with HGPS usually appear normal at birth. Profound failure to thrive occurs during the first year. Characteristic facies, with receding mandible, narrow nasal bridge and pointed nasal tip develop. During the first to third year the following usually become apparent: partial alopecia progressing to total alopecia, loss of subcutaneous fat, progressive joint contractures, bone changes, nail dystrophy, and abnormal tightness and/or small soft outpouchings of the skin over the abdomen and upper thighs, and delayed primary tooth eruption. Later findings include low-frequency conductive hearing loss, dental crowding, and partial lack of secondary tooth eruption. Additional findings present in some but not all affected individuals include photophobia, excessive ocular tearing, exposure keratitis, and Raynaud phenomenon. Motor and mental development is normal. Death occurs as a result of complications of severe atherosclerosis, either cardiac disease (myocardial infarction) or cerebrovascular disease (stroke), generally between ages six and 20 years. Average life span is approximately 13 years [38].

### **13. PHACES Syndrome**

It is characterized by children with segmental facial hemangiomas of infancy and one extracutaneous manifestation comprising PHACES (posterior fossa malformation, arteriovenous malformations, cardiac/aortic defects, eye anomalies, and sternal defect). Otolaryngic

problems were evaluated with physical examination, audiogram, swallow evaluation, polysomnography, and laryngoscopy. Otolaryngic abnormalities included middle ear atelectasis, tympanic membrane hemangiomas with conductive hearing loss, skin and cartilage ulceration, dysphagia, and airway hemangiomas with stridor. Diagnosis of PHACES requires awareness of the association of facial hemangiomas of infancy with systemic and airway problems. Otolaryngology-related manifestations of PHACES are not commonly described, and management should be tailored to the individual patient [39].

#### 14. Leopard Syndrome

Clinical manifestations of leopard syndrome include lentigines, ocular hypertelorism, mental and growth retardation, deafmuteness, and several patches of hair loss on her scalp [40].

#### D- Infections

In a study, syphilis and chickenpox were found the common antenatal associated infections with deafness [1].

##### 1. Lyme Disease

Lyme disease is an infection that starts with a tick bite. The disease has a variety of symptoms, including changes affecting the skin, heart, joints and nervous system. It is also known as borrelia or borreliosis. Neuro borrelia is the commonest complication of Lyme disease. About 15 per cent of people with Lyme disease develop problems with the nervous system, or so-called neuro borrelia, between one and five weeks after the tick bite. The central nervous system is affected and the symptoms that result may be very mixed and not specific. The symptoms often begin with back pain, typically between the shoulder blades and in the neck like a slipped disc. The pain worsens at night. Distorted feelings around the area of the bite. The nerves become numb, especially in the face. This may occur at any time up to four weeks after the

pain began. A facial palsy with weakness of the muscles on one or both sides of the face may develop. Sometimes neuro borrelia may present as meningitis, with fever, headache and stiffness in the neck. In very rare cases, the disease may become chronic, with a slowly developing destruction of the nervous system, numbing, partial hearing impairment, depression and the development of dementia. Neuro borrelia demands immediate treatment, usually with an admission to hospital [41].

##### 2. Varicella-zoster Virus

Otological complications of varicella-zoster syndrome (*Ramsay-Hunt syndrome*) include facial paralysis, tinnitus, hearing loss, vertigo, dysgeusia, and skin rash. The lower cranial nerves sometimes are affected by this neuritis [42].

##### 3. HIV Disease

**a. Kaposi's Sarcoma (KS):** The most common malignancy associated with HIV disease is KS, an idiopathic multiple sarcoma of the skin. KS occurs in 43% of homosexual or bisexual men with advanced HIV disease, only 4% of injection drug users, and essentially no hemophiliacs. Although considered an opportunistic neoplasm, KS can manifest early in the patient's course with HIV infection, and may be the first clinical manifestation of their immunodeficiency. The typical HIV-associated KS lesion is pink or purple, not tender, and macular or slightly raised or nodular, and can occur on both cutaneous and mucosal surfaces [43].

**b. Non-Hodgkin's Lymphoma:** NHL is the second most common malignancy associated with HIV disease. Most patients have fever, night sweats, and significant weight loss. NHL appears late in the course of HIV disease, often after KS and opportunistic infections. The histopathologic findings are variable, but the majority of these lymphomas are high grade. Treatment consists of aggressive systemic chemotherapy. HIV-infected patients with advanced disease have little tolerance for radiation therapy and often develop severe ref-

ractory mucositis even following small radiation doses to the upper aerodigestive tract [43].

**c. Lymphoid Hyperplasia:** The generalized proliferation of lymphoid tissue commonly associated with HIV disease often affects Waldeyer's ring (adenoids, lingual tonsils, and faucial tonsils). This association is so striking that adenoidal hypertrophy in a nonpediatric setting, even in an otherwise asymptomatic patient, should alert the clinician to a possible underlying HIV infection. The lymphoid hyperplasia found in the nasopharynx in these patients is apparently a manifestation of the HIV-associated lymphoid hyperplasia, seen in the peripheral lymph nodes as persistent generalized lymphadenopathy, and has a similar appearance on histopathologic examination [43].

**d. HIV-Associated Conditions in the External Ear:** The external ear includes the pinna and the external auditory canal (EAC). Even though the pinna and EAC are both specialized and distinct parts of the ear, their proximity and tissue similarity result in similar pathologic processes. Skin pathology commonly found in HIV-infected patients frequently occurs in both sites. The processes most commonly reported include seborrheic dermatitis and KS [43].

**e. Seborrheic Dermatitis:** As HIV disease progresses, up to 83% of patients develop extensive seborrheic dermatitis, often involving the face, scalp, and, less commonly, the periauricular region. Patients with seborrheic dermatitis of the external ear may present with recurrent superinfections of the involved skin, in some cases including the external ear. Treatment of the involved skin with a commercially available dandruff shampoo as directed and the use of a topical steroid usually control these lesions [43].

**f. Kaposi's Sarcoma in the External Ear:** KS can arise either on the pinna or in the EAC. More severe symptoms, including conductive hearing loss, may arise if the tumor extends onto the tympanic membrane (TM) or into the middle ear. The carbon dioxide laser can excise canalicular KS. With TM involvement, however, the argon laser may spare more of the normal tissue, making a TM perforation less likely [43].

**g. HIV-Associated Conditions in the Middle Ear:**

The most common otologic problems reported in HIV-infected patients are serous otitis media and recurrent acute otitis media. Clinicians should obtain mycobacterial, fungal, and routine bacterial cultures to optimize anti-infectious therapy. Medical management usually leads to rapid resolution of these infections. Acute inflammation of the mastoid air cells can occur with any middle ear infection, but coalescing suppurative mastoiditis, with its bony sequestration and abscess formation, is relatively rare. This infection can cause a subperiosteal abscess clinically manifested by protrusion of the anterior-inferior external ear, or intracranial extension, including epidural abscess or temporal lobe abscess [43].

**h. HIV-Associated Sensorineural Hearing Loss:**

Sensorineural hearing loss, both unilateral and bilateral, occurs in 21 to 49% of HIV-infected patients. The majority of such patients have had a sensorineural hearing loss that steadily worsens with increasing frequencies, becoming moderate at high frequencies, but speech discrimination is usually near normal. A possible etiology is a primary infection by HIV of either the central nervous system (CNS) or peripheral auditory nerve [44].

**i. HIV-Associated Vertigo:** Vertigo can occur in the HIV-infected patient. When present, it is usually concurrent with a multitude of other neurologic symptoms. Vertigo is frequently a symptom of subacute encephalitis or HIV disease dementia complex. HIV may directly affect the vestibular and auditory systems; however, verification requires further study [44].

**j. HIV-Associated Facial Nerve/Central Nervous System Facial-Paralysis Syndromes:**

Facial nerve paralysis is more common in the HIV-infected patient than in the immunocompetent patient. According to one report, up to 7.2% of patients with HIV disease will have either unilateral or bilateral facial paralysis. In the majority of these patients, CNS processes are the cause of the facial paralysis; CNS toxoplasmosis is the most common identifiable cause, followed by HIV encephalitis and CNS lymphoma [44].



**-Idiopathic or Bell's Palsy:** Idiopathic facial nerve palsy, or Bell's palsy, is the single most common diagnosis given for HIV-infected patients with seventh nerve paralysis. The leading theory for the cause of Bell's palsy is an infection of the facial nerve by herpes simplex virus. Researchers believe that the immunocompromise caused by the HIV infection allows greater incidence of viral infection and associated facial paralysis. The outcome in this patient group, like that in the general population, is excellent. The nerve usually recovers completely in 3 weeks to 3 months. Standard therapy consists of corticosteroids such as prednisone, 60 mg PO orally every day for 4 days and then tapered over 10 days, and acyclovir, 200 mg orally 5 times a day, for all patients with Bell's palsy, if seen during the first 2 weeks of presentation [43].

**-Herpes Zoster:** Herpes zoster infection, or the Ramsey Hunt syndrome, occurs more commonly in HIV-infected than in non-HIV-infected patients. This syndrome results from a chronic herpetic infection of the geniculate ganglion, which acutely results in painful herpetic vesicles in the distribution of the sensory component of the facial nerve along with facial palsy, which occasionally is permanent. Symptoms tend to be more severe in the HIV-infected than in the non-HIV-infected patient, and response to medical therapy is less predictable [43].

**k. HIV-Associated Cutaneous Lesions:** Cutaneous lesions of the nose or face are common presenting symptoms of HIV infection. KS, herpetic infection, and seborrhea-like dermatitis are three such conditions. While these are often primarily cosmetic problems, KS in particular can become symptomatic or widely disseminated [43].

**-Seborrheic Dermatitis:** Facial seborrheic dermatitis also occurs in HIV-infected patients. Initially observed in 22% of the population with advanced HIV disease, this rash can occur anywhere in the head and neck, but seems to have a predilection for the postauricular, nasal, and malar regions. The malar rash can resemble the butterfly pattern of systemic lupus erythematosus. Symptoms are predominantly cosmetic and a biopsy is rarely indicated. Although we recommend tre-

atment with topical corticosteroids, some cases are refractory [43].

**-Herpes Infections:** Either herpes simplex or herpes zoster may cause the giant herpetic nasal ulcer. Although characteristically originating in the nasal vestibule, they often extend onto the facial skin, sometimes reaching diameters of up to several centimeters [43].

**l. HIV-Associated Nasal and Paranasal Sinus Problems:** Nasal and paranasal sinus problems are among the most common presentations of HIV disease. Although the percentage of patients with symptoms specifically localized to the nose and paranasal sinuses is not known precisely, prospective studies of patients infected with HIV described a 30 to 68% prevalence of sinusitis. Other well-documented sinonasal conditions in the HIV-infected population include cutaneous lesions, nasal obstructions, allergy and allergic rhinitis, inflammatory sinusitis, and neoplasms [43].

**-Nasal Obstruction:** Nasal stuffiness, a common symptom during HIV infection, has a wide-ranging differential diagnosis that includes adenoidal hypertrophy, allergic rhinitis, chronic sinusitis, and neoplasms of the nose, paranasal sinuses, or nasopharynx. History and physical examination, including indirect laryngoscopy, usually suffice for evaluation of obstructive symptoms [43].

**-Allergic Rhinitis:** Curiously, although depressed cellular immunity results in decreased total lymphocyte and helper T-lymphocyte counts, polyclonal B-cell activation produces increased circulating immune complexes with increased production of IgA, IgG, and IgE. This excessive IgE production is associated with increased IgE-mediated allergic symptoms, including allergic rhinitis [43].

**m. HIV-Associated Oral Cavity lesions:** One of the most common regions of the head and neck in which HIV-related pathology occurs is the oral cavity. The spectrum of oral diseases includes infectious, benign inflammatory, neoplastic, and degenerative processes.

**-Pharynx and Larynx:** Because of the anatomic proximity and functional relationships, many of the conditions described in the oral cavity also occur in the pharynx and larynx.

These infections, inflammatory conditions, and neoplastic processes can all produce morbidity, and occasionally mortality, when presenting in this vital anatomic region of the upper aerodigestive tract [43].

**-Candidiasis:** Candidal infection can occur in the oropharynx, hypopharynx, and larynx, and usually results in severe odynophagia that often interferes with deglutition. When the larynx is affected, hoarseness is a prominent feature. Some degree of aspiration also occasionally results due to interference with normal laryngeal function. When the hypopharynx and larynx are affected, the clinician must entertain the possibility of esophageal candidiasis, and obtain appropriate diagnostic studies including barium swallow or esophagoscopy. Treatment in these cases usually requires systemic antifungal agents and response to therapy is less predictable. In general, candidiasis of the pharynx, larynx, and esophagus is associated with advanced HIV disease and CD4 counts less than 200 [43].

**-Herpes Simplex and Cytomegalovirus:** Herpes simplex lesions can occur in the pharynx and larynx. CMV infection has also been observed with increasing frequency. The clinical findings are often nonspecific; however, biopsy with histopathologic examination and viral culture will usually confirm the diagnosis. Systemic antiviral agents such as ganciclovir or foscarnet can produce symptomatic improvement for these patients. This diagnosis should be considered when empiric therapy for other infectious and inflammatory conditions is ineffective and malignant conditions have been excluded [43].

**-Recurrent Aphthous Ulcerations:** As in the oral cavity, recurrent aphthous ulcerations also occur in the pharynx, manifesting as giant aphthous ulcers (> 2 cm) in the oropharyngeal region, especially the tonsillar pillars, tonsils, and base of the tongue. There are also large aphthous lesions in the hypopharynx and nasopharynx. Treatment parallels that in the oral cavity. Severe symptoms associated with lesions in the pharynx and larynx, however, usually necessitate aggressive medical therapy and early nutritional support [43].

**-Acute Adult Epiglottitis:** Acute adult epiglottitis has been observed in HIV-infected patients. As in the non-HIV-infected population, this condition is serious and potentially life-threatening. Symptoms usually consist of severe sore throat, odynophagia, laryngeal tenderness, fever, and malaise. Drooling, stridor, and airway obstruction are usually late symptoms in adults. Simple examination of the oral cavity and oropharynx is often unimpressive; however, the lack of clinically apparent disease in the setting of such severe symptoms should raise the suspicion of this potentially grave diagnosis. Tenderness to palpation and movement of the larynx is almost universal [43].

**-Benign Lymphoid Hyperplasia:** Benign lymphoid adenotonsillar hyperplasia in Waldeyer's ring can often result in nasal airway obstruction, eustachian tube obstruction, and occasionally, oropharyngeal airway compromise. Even the lingual tonsillar tissue at the base of the tongue can become tremendously enlarged, resulting in dysphagia and obstructive apnea, especially when the patient is recumbent. Although antibiotic therapy occasionally relieves these symptoms, acute or chronic bacterial infection rarely underlies this problem. Surgery is the best alternative when this condition becomes symptomatic [43].

**-Kaposi's Sarcoma and Non-Hodgkin's Lymphoma:** KS and NHL can occur in the pharynx and larynx. The ever-present risk of airway obstruction and interference with deglutition makes early aggressive therapy vital. Despite the mucositis that often accompanies radiation therapy, this treatment is the primary therapeutic tool for malignancies in this region. For tumors encroaching on the airway, prophylactic tracheotomy is worth considering because the acute inflammatory response accompanying radiation will often result in total airway obstruction before the tumor begins to regress. A nasal feeding tube is also helpful to ensure nutrition [43].

**-Salivary Glands Salivary gland disease:** It is fairly common in HIV-infected patients. These patients often complain of xerostomia and have diffuse glandular swelling. The single process unique to HIV infection in the parotid gland is the lymphoepithelial cyst. Neck

an enlarging neck mass occurs in up to 91% of HIV-infected patients with head and neck manifestations. The traditional work-up of the adult neck mass is based on the need to rule out malignancy; however, the evaluation of a neck mass in the HIV-infected patient is complicated by the frequency of numerous opportunistic infections and neoplasms unique to HIV disease. The etiology of neck masses in this specific population can be divided into the following categories: HIV lymphadenopathy, infectious processes, parotid disease, and neoplasms [43].

#### 4. Syphilis

Syphilis is caused by the spirochete *Treponema pallidum* and is characterized by 3 sequential clinical, symptomatic stages separated by periods of asymptomatic latent infection. Common manifestations include genital ulcers, skin lesions, meningitis, aortic disease, and neurologic syndromes. Diagnosis is by serologic tests and adjunctive tests selected based on the disease stage. Penicillin is the drug of choice. Syphilitic ocular and otic manifestations can occur at any stage of the disease. Ocular syndromes can affect virtually any part of the eye; they include interstitial keratitis, uveitis, chorioretinitis, retinitis, retinal vasculitis, and cranial nerve and optic neuropathies. Ootosyphilis may affect the cochlea (causing hearing loss and tinnitus) or vestibular system (causing vertigo and nystagmus). Reports of cases of primary and secondary syphilis are increasing in the United States, particularly in urban areas and among homosexual men. While primary syphilis poses little diagnostic difficulty, many physicians are unfamiliar with the multisystem nature of secondary lues. Patients who have secondary syphilis commonly present with systemic signs, skin rash, mucous membrane lesions and generalized adenopathy. Less commonly, secondary syphilis may occur as acute meningitis, sensorineural hearing loss, iritis, anterior uveitis, optic neuritis, Bell's palsy, gastropathy, proctitis, hepatitis, pulmonary infiltration, nephrotic syndrome, glomerulonephritis, periostitis, tenosynovitis and polyarthrititis. The diagnosis of secondary syphilis is easily confirmed. Its various manifestations are readily treated with penicillin and, if treated early, are entirely reversible [45].

#### 5. Epidermodysplasia Verruciformis

It is a rare, inherited disorder in which there is widespread and persistent infection by multiple subtypes of human papilloma virus, tinea versicolor-like lesions and plaques, and frequently malignant manifestations. Sometimes the patients have classical skin lesions together with neurological manifestations and deafness [46].

#### E- Allergic Skin Diseases

A stuffy nose, runny nose, polyps (growths) in the nose, itching and puffy eyes, frequent sore throats, asthma, skin rashes, and behavioral problems such as hyperactivity in children may be symptoms of allergy. Symptoms may occur in almost all systems of the body, including ears.

**Allergy and the Ears:** Outer Ear symptoms that may be attributed to allergy include chronic itching or frequent infections of the ear canal. Middle Ear symptoms may include repeated ear infections and long-standing fluid behind the eardrum are often due to allergy. Both of these are more common in children. Inner Ear symptoms attributed to allergy may include dizziness, ear fullness and pressure, tinnitus or head noise, and sensorineural hearing loss especially food allergy. Meniere's disease in one or both ears may sometimes be aggravated by allergies [47, 48, 49].

#### Types of Allergies

**Inhalant Allergy:** Symptoms of inhalant allergy are caused by reactions to allergens that enter the body via the respiratory tract. They may develop with recurrent or prolonged exposure to the allergen. These can be pollens, dust, molds, animal dander, or other substances breathed in through the nose. Symptoms of inhalant allergy may be year-round or seasonal. High fever is a form of inhalant allergy due to weed pollen released in the fall. When the nose or lungs come in repeated contact with allergens, the immune system of allergic patients makes a high level of a blood protein, or antibody called Immunoglobulin E (IgE). The IgE attaches to special allergic cells, called mast cells, found through-

hout the body. When the allergen enters the respiratory tract, a change occurs in the mast cells outer membrane causing the cell to release inflammatory substances called mediators which produce allergic symptoms. One of the best known mediators is called histamine; it causes itching, mucous secretion, and some congestion of tissue. This is why an antihistamine is frequently prescribed for allergy symptoms. Intranasal steroids relieve nasal symptoms and ocular itch in allergic rhinitis. Itchy ear and palate are also common and bothersome symptoms but have received little attention in clinical trials of allergic rhinitis. Mometasone furoate nasal spray can effectively treats itchy ear and palate in individuals with seasonal allergic rhinitis. Itchy ear and palate is a relevant end point for future clinical trials of allergic rhinitis [47].

**Food Allergies:** Often, common foods that are eaten frequently are the ones that cause symptoms of food allergy. Allergens taken into the digestive tract such as wheat, fruit, shellfish and dairy products can cause allergic symptoms such as nasal congestion, hives, or ear infections. Non-food substances that are ingested may cause similar symptoms. These would include medicines such as penicillin or sulfa, or chemicals such as food preservatives [47].

**Contact Dermatitis:** Contact dermatitis is a rash or swelling caused by direct contact of an allergen with the skin. Poison ivy, nickel earrings, wool shirts or certain ear drops may stimulate a cell called the T-lymphocyte to release allergic mediators which affect the skin. The resulting rash may last many weeks or months after exposure. It was described a patients with allergic contact dermatitis to cochlear implant (polyethylene terephthalate mesh) [47].

**Autoimmune Inner Ear Disease (AIED):** AIED is believed to be caused by the body's immune system attacking the inner ear and damaging the hearing and sometimes the balance nerve. Autoimmune disease occurs when the body produces an immunological or allergic reaction to itself, instead of reacting to an external substance. In most cases, we don't know why this occurs. Some patients with AIED have signs of other diseases caused by an overly active immune system arth-

ritis, skin rash, allergy, etc. AIED is characterized by the rapid progression of hearing loss often over a period of several weeks to a few months. About 30% of people with AIED will present with symptoms of *Meniere's* disease fluctuating sensorineural hearing loss, episodic spinning vertigo, tinnitus, and fullness in the involved ears. The hearing loss in these individuals will progress at a much more rapid rate than we see with typical *Meniere's* disease. At other times, AIED will present with a sudden hearing loss in one or both ears. Usually AIED produces hearing loss in both ears, although it may present initially in one ear and months to years later develop in the second ear [47, 48].

Specific allergens may be diagnosed by skin testing, blood tests, or a challenge test. Blood tests are also used to aid the diagnosis of AIED. Mild allergic symptoms require no specific test for diagnosis, and can be well controlled with some combination of antihistamines, prescription nasal sprays, decongestants, and avoidance of known allergens. Most of the prescription nasal sprays for allergy are mild topical steroids. They can be very effective for most nasal allergy symptoms, including congestion, dripping and itching. Side effects include occasional nosebleeds, or nasal crusting. Decongestants shrink swollen tissue such as the mucus membrane of the nose. They are often combined with antihistamines. Side effects include insomnia, rapid heartbeat, and potential prostatic obstruction in men. Excellent non-specific measures to avoid contact with allergens may include the use of a central or room-sized air purifier equipped with a high efficiency particulate filter to remove the microscopic sized allergens such as pollen or mold spores. Impermeable mattress and pillow covers to lessen exposure to dust mites are inexpensive and quite useful. Information on other products such as those designed to make animal dander less allergenic and kill molds that grow in living spaces can be obtained from your allergist or through environmental supply manufacturers [47].

**Pruritic external auditory canals:** Patients with isolated pruritic external auditory canals (EACs) are common in the practice of otolaryngologists. Most otolaryngologists probably treat pruritic EACs with topical acetic



acid (0.25%) with or without hydrocortisone. Although the use of this medication is efficacious in some patients, there are some patients who continue to have symptoms. The use of low-potency topical steroid ointments is another effective therapy for patients with pruritic EACs. A new class of topical immune modulators was approved by the Food and Drug Administration (FDA). Topical tacrolimus and pimecrolimus are ointments indicated for atopic dermatitis and have been used successfully in the treatment of contact dermatitis. The mechanism of action of pimecrolimus is not clearly known. It has been observed that pimecrolimus binds to macropilin-12 and inhibits calcineurin. Therefore, it inhibits T-cell activation by blocking the transcription of early cytokines, including of interleukin (IL)-2, IL-4, IL-10, and interferon gamma. Another mode of action of pimecrolimus is that it prevents the release of inflammatory mediators and cytokines from mast cells after stimulation by antigens or immunoglobulin E. Pruritis of the ears is a complex problem with many different etiologies. Differential diagnosis of this disease process includes carcinoma of the EAC, contact dermatitis, seborrheic dermatitis, psoriasis, dermatomycosis, or dermatophytid reaction. Depending on the etiology, various treatments have been found to be successful. Various authors have reported success with steroid-containing solutions. Some authors believe that most patients with pruritic ears probably suffer from allergic contact dermatitis. On the basis of this belief, they treated a group of patients with pruritic EACs with topical pimecrolimus 1% ointment and achieved a 94% success rate. Allergic contact dermatitis in the ear likely occurs from contents of hair care products. Surfactants in shampoo such as cocamidopropyl betaine and its purported allergen amidoamine are among the top 20 most frequently patch-test positive allergens. Preservatives are another large class of molecules that are common causes of contact dermatitis and are found in nearly all shampoos and conditioners. In considering that many hair care products, especially shampoos and conditioners, come in contact with the EAC, it is not unusual that contact dermatitis will occur in the EAC. The thin skin of the EAC is normally protected by the natural oils and the cerumen produced by glands in

the EAC skin. When the protective layers of the EAC skin are removed by the use of cotton-tipped applicators (Q-tips) or by other means, the thin EAC skin is vulnerable to the penetration of haptens. With multiple sensitizations, an allergic dermatitis occurs, which leads to an inflammatory process in the EAC skin. The inflammation in the EAC, in turn, may lead to a reduction or halt in the secretion of the natural oils and cerumen. This leads to a vicious cycle seen in these patients with a lack of cerumen, a dry EAC, and continued contact dermatitis. Histopathologically, the EAC skin in patients with acerumenosis has hyperkeratosis, parakeratosis, and acanthosis with intercellular edema. Keratinized material is seen in apopilosebaceous orifices. The treatment of contact dermatitis is dependent on avoidance of the allergen and the treatment of the associated inflammation in the skin. Allergen avoidance is important in the maintenance treatment of patients with pruritic EACs [49].

## F- Pigmentary Disorders

**1. Waardenburg syndrome:** In this syndrome, the dystopia cantorum was the most frequent feature, followed by the white streak on the skin of the forehead, hypopigmentation of the iris and retina and deafness. Three patients had sensorineural hearing loss (12.5%), associated with white forelock and achromatic spots confluent by the body. This study shows the importance of the ophthalmologist in aiding the diagnosis of this rare genetic condition, since it includes ocular disorders such as telecanthus, hypopigmentation of the iris and retina. The cantorum dystopia is the main diagnostic criterion to differentiate type I and II syndrome and should be done by a trained ophthalmologist. The families are in medical monitoring, receiving genetic guidelines and care related to eye protection [50].

**2. Vogt-Koyanagi-Harada's syndrome:** It is a rare disease that affects tissues containing melanocytes, such as the eyes, central nervous system, inner ear and skin. Some ethnic groups have a higher probability of developing the disease, including Asians, Indians and Latin Americans and females are affected more often. The disease probably has autoimmune etiology, with aggression occurring on

the surface of melanocytes by promoting inflammatory reaction in which T lymphocytes predominate. The allele most often found in association with this disease is HLA DRB1\*0405. Clinical manifestations are divided into four stages: prodromal, uveitic, chronic and recurrent. Otorhinolaryngological symptoms occur during the uveitic stage and are characterized by bilateral sensorineural hearing loss, tinnitus and vestibular symptoms. Diagnosis is made according to the diagnostic criteria for the disease. Treatment is primarily with corticosteroids [51].

### G- Medications and Poisoning

The FDA said it found 29 reports of sudden hearing loss, sometimes temporary, associated with the erectile dysfunction agents after scouring the Adverse Event Reporting System. There have also been cases of sudden hearing loss reported in patients using Revatio (sildenafil) for pulmonary arterial hypertension. Ototoxic drugs, which are medications that are toxic to the ear, have the potential to cause permanent or temporary hearing loss. Approximately 200 prescription and over-the-counter drugs are ototoxic, including some antibiotics, chemotherapy medications, anesthetics, cardiac medications, glucocorticosteroids, mood altering drugs, and some vapors and solvents. An ototoxic hearing loss happens when someone takes or is given a drug that causes loss of hearing as one of its side effects, such as some antibiotics, chemotherapy drugs, and anti-inflammatories. Ototoxicity ("ear poisoning") is due to exposure to drugs or chemicals that damage the inner ear or the vestibulo-cochlear nerve, which sends balance and hearing information from the inner ear to the brain. Ototoxicity can result in temporary or permanent disturbances of hearing, balance, or both. Many chemicals have ototoxic potential. Certain drugs can affect hearing by damaging the nerves involved in hearing. Usually this occurs when large or toxic doses are used but may also occur with lower doses. Antibiotics including aminoglycosides (gentamicin, vancomycin), erythromycins, and minocycline, diuretics including furosemide and ethacrynic acid, salicylates (aspirin) and nonsteroidal anti-inflammatories (NSAIDs) such as ibupro-

fen and naproxen, antineoplastics (cancer drugs) can lead to hearing loss [52].

### Lead poisoning

Lead affects every one of the body's organ systems, especially the nervous system, but also the bones and teeth, the kidneys, and the cardiovascular, immune, and reproductive systems. Hearing loss and tooth decay have been linked to lead exposure, as have cataracts. Intrauterine and neonatal lead exposure promote tooth decay. Aside from the developmental effects unique to young children, the health effects experienced by adults are similar to those in children, although the thresholds are generally higher. Chronic poisoning usually presents with symptoms affecting multiple systems, but is associated with three main types of symptoms: gastrointestinal, neuromuscular, and neurological. Central nervous system and neuromuscular symptoms usually result from intense exposure, while gastrointestinal symptoms usually result from exposure over longer periods. Signs of chronic exposure include loss of short-term memory or concentration, depression, nausea, abdominal pain, loss of coordination, and numbness and tingling in the extremities. Fatigue, problems with sleep, headaches, stupor, slurred speech, and anemia are also found in chronic lead poisoning. A "lead hue" of the skin with pallor is another feature. A blue line along the gum, with bluish black edging to the teeth, known as Burton line is another indication of chronic lead poisoning. Children with chronic poisoning may refuse to play or may have hyperkinetic or aggressive behavior disorders [53].

### H- Neoplasms

**1. Nodular Mastocytosis:** Mastocytosis refers to a group of disorders characterized by the pathologic proliferation of mast cells. Nodular mastocytosis is characterized by disseminated nodular lesions, myelodysplastic syndrome, and a c-kit V560G receptor mutation. Sometimes ear pruritus and hearing loss can occur [54].

## 2. The Nevus Sebaceus of Jadassohn (SNJ):

It is a congenitally-occurring, hamartomatous disorder of the skin and its adnexa of infrequent occurrence. This presentation of five cases emphasizes the smooth, waxy, yellow-brown lesion's progression into a thickened sebaceous tumor of premalignant predilection. The incidence of neoplastic degeneration of these hamartomatous nevi may be as high as 30% with the capacity of metastasis occasionally reported. Because of malignancy risks as well as cosmetic considerations, early surgical removal is recommended. Previously unreported problems of dysphagia and malnutrition secondary to pulsion diverticulum at the esophageal inlet and cleft palate, obliterative aural stenosis with associated conductive hearing loss are documented. Regardless of SNJ's occurrence as either an isolated lesion or as the fully developed syndrome, including mental retardation and epilepsy, this congenital malformation of the skin, its hair, and sebaceous glands presents rare and histologically intriguing problems for the practitioner [55].

**3. Fibrous Dysplasia:** It is a fairly common, localized misdifferentiation of the bone-forming mesenchyme affecting a single or many bones, in which skeletal aberrations represent the cardinal feature, but in which certain endocrinopathies, abnormal pigmentation of skin and mucous membrane, and occasionally other abnormalities form part of the entire disease process. The craniofacial skeleton is one of its predilective sites and therefore the temporal bone may become involved. In such instances the disease manifests itself with 1) progressive loss of hearing, 2) increasing obliteration of the external ear canal, and 3) enlargement and distortion of the temporal bone [56].

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