AUDIOLOGICAL EVALUATION IN AUTO-IMMUNE SKIN DISEASES: A CLINICAL STUDY OF 124 PATIENTS

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HOW TO CITE THIS ARTICLE:

A. Sesha Prasad, M. Sreedhar Rao, A. V. S. Hanumantha Rao, D. Satyanarayana, S. Muneeruddin Ahmed, M. Mahendra Kumar. "Audiological Evaluation in Auto: Immune Skin Diseases- A Clinical Study of 124 Patients". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 30, April 13; Page: 5128-5137, DOI: 10.14260/jemds/2015/749

ABSTRACT: INTRODUCTION: 124 patients with common dermatological conditions with an autoimmune etiology are evaluated for hearing, irrespective of complaints of hearing loss. Auto-immunity is described as an etiology of Sudden or Progressive Sensory neural Hearing Loss; similarly autoimmunity is described as an etiology for many skin diseases like Psoriasis, Dermatomyositis etc., and the present study evaluates hearing thresholds in patients with auto-immune skin disorders. Autoimmunity is the etiology for both these conditions, causes many changes in the micro vasculature of the various organs and produces immune complexes in the body. Hence evaluation of other organs in the presence of clinically evident autoimmune disease in one organ will guide the clinician for early diagnosis of auto immunity. So the patients with alopecia areata, Dermatomyositis, Psoriasis, Systemic sclerosis, Systemic Lupus Erythematoses, Vitiligo, Epidermolysis Bullosa and scleroderma are included in the present study for hearing evaluation. MATERIALS AND METHODS: 124 Patients attending the department of Dermatology and diagnosed with the following diseases are included in the present study; 1. Alopecia areata 2. Dermatomyositis 3. Psoriasis 4. Systemic sclerosis 5. Systemic Lupus Erythematoses 6. Vitiligo 7. Epidermolysis Bullosa. This is a prospective study conducted at GGH, Kurnool, and Andhra Pradesh. The diagnosis of the clinical entities included in this study is done according to clinical and Histopathological findings. The patients are referred from the Department of Dermatology for evaluation. After thorough history taking, the Patients are subjected for ENT examination. Pure Tone Audiometry at 250, 500, 1, 000, 2, 000, 4, 000, 6, 000 and 8, 000 Hz is done followed by Impedance audiometry; including tympanometry and acoustic reflexes are done. **CONCLUSION:** Audiological evaluation in autoimmune skin diseases showed occurrence of hearing disability with statistical significance justifying adequate protocol of investigation in all such patients. KEYWORDS: Psoriasis; hypercoagulability; inflammation, SSNHL, autoimmune disease, Dermatomyositis, SLE, Scleroderma and Epidermolysis Bullosa.

INTRODUCTION: Many papers related to assessment of hearing in auto-immune diseases are published but studies related to incidence of hearing disability in auto-immune skin disorders are very few. The aim of this study was to assess cochlear functions and hearing evaluation in patients with psoriasis and other autoimmune diseases with skin involvement.¹ In 1979 Mc Cabe gave his first description of hearing impairment in auto-immune diseases.² 4 This was followed by studies to show loss of hearing in patients like ankylosing spondylitis, Rheumatoid arthritis, Behcet's disease, Sjogren's syndrome, SLE and Polyarteritis nodosa. Psoriasis is defined as a chronic disease with Papulo-squamous skin lesions which are circumscribed, Erythematous, scaling, thickened plaques. The Etiology of Psoriasis is not known; recent researches have shown the pathogenesis of psoriasis as a long standing, immune mediated, inflammatory disorder.

Few researchers have demonstrated CD8 and T cell predominant in the epidermis of these patients. The correlation between resolution of the disease and reduction of CD8 and T cells is observed.²⁻⁷ Autoimmune diseases show systemic vascular involvement affecting all the organs. They will manifest in sudden sensorineural hearing loss (SSNHL); likewise result in changes in kidney and coronary system.⁸ Psoriasis is a common autoimmune disease occurring in 2% of the population worldwide.⁹ Thick plaques occur on scalp, sacrum and extensor surfaces of knees and elbows. Acute lesions include small guttate lesions, erythroderma, and Psoriatic arthritis and nail involvement.¹⁰

Auto-immune causes are recently added as etiological factors in inner ear diseases resulting in Sudden Sensorineural Hearing Loss (SSNHL). It usually presents bilaterally, or may present as slow progressive SNHL over few weeks to months. In few patients may be associated with symptoms of imbalance and tinnitus. When recognized early, starting steroids and /or immunosuppressive agents will give recovery at least in mild hearing loss patients.¹¹ Alopecia areata is an auto-immune disease of hair loss of scalp and/ or body without scar formation. Usually affects scalp with single or multiple patches. Increase in telogen follicles and peribulbar infiltration of lymphocytes is characteristic feature Histopathological studies. Corticosteroids are the most popular drugs for the treatment of this disease. In view of the systemic involvement of organs due to autoimmunity audiological evaluation will reveal involvement of hair cells of cochlea irrespective of the patient giving the history of deafness. The present study is conducted to know the incidence of hearing impairment and evidence of hair cell damage in patients with autoimmune skin diseases.

MATERIALS AND METHODS: 124 patients attending the department of Dermatology are advised to attend ENT OPD for evaluation of hearing. The patients diagnosed as autoimmune skin disorders are alone included. All patients are confirmed of their diagnosis by Hematological and Histopathological investigations. Patients with the following diseases are included in the present study. They are: 1. Alopecia areata-28 2. Dermatomyositis-08 3. Psoriasis-36 4. Systemic sclerosis-06 5. Systemic Lupus Erythematoses-10 6. Vitiligo-32 7. Epidermolysis Bullosa-04 8. Patients are assessed by history taking regarding their hearing capabilities followed by pure tone audiometry. Pure tone average of 500, 1000, 2000, 4000, 6000 and 8000 Hz was used to classify the losses as mild (26-40 dB), moderate (41-70 dB), severe (71-90 dB), profound (>90 dB), or total. Using 25 dB (hearing level) as normal hearing threshold allows a universal use of this form of hearing measurement, even in cases with bilateral involvement when the use of contra lateral side as reference is not possible. Patients are then subjected to Impedance audiometry to record Tympanogram and middle ear pressures. Acoustic reflexes are also recorded. A 250Hz test probe is used with the impedance audiometer arphi manufacture Model VI. he treatment prescribed by the dermatologist for these patients, duration of treatment and use of steroids is not taken into consideration because, the basic idea of this paper is to evaluate hearing thresholds of the Patients to know if there is any hair cell damage.

Inclusion Criteria:

- 1. Patients with 8 common skin diseases mentioned above are included.
- 2. Patients aged between 12 years to 60 years are included.
- 3. Disease severity was evaluated by the PASI (Psoriasis Area and Severity Index).
- 4. Informed consent was obtained from all participants.
- 5. Patients with no history of ototoxic drugs, noise exposure, ear surgery, perforated tympanic membrane, Meniere's disease, cranial trauma, metabolic diseases are alone included.

Exclusion Criteria:

- 1. Patients with Chronic Suppurative Otitis Media.
- 2. Presence of a flat Tympanogram or absence of acoustic reflexes at 1 kHz with contralateral stimulation.
- 3. An air-bone gap of 5 dB at any frequency.
- 4. Patients with history of cardiovascular disease, cerebro vascular complications, peripheral artery disease, renal insufficiency, syphilis, Meniere's disease and other vestibular syndromes, infections involving the inner ear, Barotrauma, or use of ototoxic drugs.

OBSERVATIONS: In the present study 124 patients (248 ears) males are 68 and 56 are females. The youngest patient is aged 14 years and the eldest 59 years; the mean age is 29.6. The age group of 20 to 50 years showed incidence of most of the skin diseases selected in this study i. e., 107 (86.29%) out of 124 patients. Table I. History of Diminished hearing is present in 76 (61.29%) patients. Among these patients loss of hearing in both the ears is present in 39 (51.31%) patients, in the right ear 21 (27.63%) patients and in the left ear 17 (22.36%) patients. Patients without history of hearing loss are 48 (38.70%); in them bilateral hearing loss is seen in 28 (58.33%), loss only in right ear 08 (16. 66%) and in left ear 11 (22.91%). Table III. History of sudden sensorineural Deafness is found 18 out of the 124 patients accounting to (14.51%). It is observed that the air conduction thresholds among the 48 (38.70%) patients who did not give history of diminished hearing, hearing threshold more than 30 dB is seen in 23 (47.91%) patients, more than 40dB is seen in 12 (25%) patients and 06 (12.5%) patients had more than 50dB loss and 07 (14.53%) patients had hearing loss between 20 to 30 dB loss. (Table 2).

Age in Years	M (68)	F (56)	Psoriasis (36)	Dermato Myositis (08)	Sclero Derma (06)	Alopecia areata (28)	SLE (10)	Vitiligo (32)	Epidermolysis Bullosa (04)
10-20	16	08	06			06		12	
20-30	18	16	11	04	02	06	03	09	02
30-40	11	09	08	04	02	09	03	07	02
40-50	10	07	08		02	04	04	02	
50-60	08	10	02			03		02	
60-70	05	06	01						
Table 1: Showing incidence of diseases according to age and sex (n=124)									

Hearing Thresholds dB loss	Psoriasis (36)	Dermato Myositis (08)	Scleroderma (06)	cleroderma Alopecia Areata (06) (28)		Vitiligo (32)	Epidermolysis Bullosa (04)	
0-15	12			07	02	09		
15-25	04			06		06	01	
25-35	06	06	03	10	03	08	01	
35-45	06	02	02	02	03	06	01	
45-55	06		01	02	01	03	01	
55-65	02			01	01			
65-75								
Table 2: Showing hearing threshold values in patients. $(n=124)$								

Taking 25dB as the base level of normal hearing 47 (37.90%) patients out of 124 had normal thresholds of hearing with 0 to 25 dB recording. (Table 2). The other 77 (62.09%) patients showed PTA averages more than 25dB. This observation is statistically significant (P-value < 0.05) i. e., 0.0005.

Disease	Bilateral (67)	Right Ear (32)	Left Ear (25)	History of Loss of hearing (76)	No history of loss of hearing (48)	
Psoriasis (36)	16	11	09	21	15	
Dermato Myositis (08)	06	01	01	06	02	
Alopecia Areata (28)	13	08	07	18	10	
SLE (10)	04	04	02	06	04	
Vitiligo (32)	21	06	05	19	13	
Epidermolysis Bullosa (04)	04			03	01	
Scleroderma (06)	03	02	01	03	03	
Table 3: showing side of involvement of the ears according to the disease. (n=124)						

76 patients out of 124 gave history of loss of hearing within a period of 3 years from the study and 48 patients gave no history of hearing loss. This is statistically significant P-value is 0.0061 (P-value is 0.05). Impedance audiometry showed normal A type curve in 83 (66.93%) patients, 26 (20.96%) patients showed C type of curve and 15 (12.09%) patients showed B type of curve. (Table 3).

Disease	Туре А (83)	Туре В (15)	Туре С (26)	Acoustic reflex threshold ipsilateral 85+/-10dB	Acoustic reflex threshold ipsilateral 95+/-10dB	Acoustic reflex threshold ipsilateral 105+/-10dB	Statistical significance of impedance audiometry P-value <0.05	
Psoriasis (36)	29	05	02	19	11	06	0.004	
Dermato Myositis (08)	05	02	01	03	01	04	0.015	
Alopecia Areata (28)	22	01	05	18	10	07	0.44	
SLE (10)	06		04	02	02	02	0.040	
Vitiligo (32)	20	04	08	19	06	07	0.002	
Epidermolysis Bullosa (04)	03		01	01	01	01		
Scleroderma (06)								
Table 4: Showing impedance audiometry measurements								

DISCUSSION: There are more than 80 recognized autoimmune diseases in the Medical literature. These result due to specific immune responses directed against structures of the self.⁽¹⁴⁾ All the features of pathogenesis autoimmunity cannot be explained by a single theory or mechanism. Environmental trigger factors like tissue damage, infections, inheritance of susceptible genes, activation of self-reacting lymphocytes of immune system and hormonal changes play a complex role leading to development of autoimmunity. At molecular level breakdown of tolerance at both T cell and B-cell level has been formulated.⁽¹⁵⁾ Elias Toubi et al in their study concluded that SSNHL is a result of multiple immune mediated disorders. Persistent lack of aCL antibody in more than half of their patients suggests that viral infection may trigger a transient phenomenon triggering aCL activity.⁽¹⁶⁾ Tamara Majovik et al noted that SNHL due to autoimmunity is a rare entity characterized by progressive slow hearing loss over a period of several weeks to months. It may present in addition to hearing loss with tinnitus aural fullness, vestibular symptoms in 50% of the patients. Lack of clinical suspicion and of specific tests for diagnosis, results in inability to undertake an epidemiological survey of autoimmune disease causing SNHL. In less than 1% of cases of SNHL the hearing loss is due to Autoimmune ear diseases (AIED). But this can be an understatement because of lack of specific diagnostic tests. AIED are potentially treatable.

To quote McCabe's original description; "the time course of the hearing loss is the best clue to AIED diagnosis;" a period of progression of the deafness over weeks or months, not hours nor days nor years. This course distinguishes AIED from sudden deafness and from age-related hearing loss. " The AIED can be primary if the pathology is restricted to one ear and secondary if it occurs in the context of a systemic AID. Progressive hearing loss more than 30dB or more at any frequency in one ear, on two serial audiograms done less than 3 months apart is defined as HL due to AIED. The present study showed 66.09% of the patients showed hearing loss. His is statistically significant with P value 0.0005. History of hearing loss is seen in 76 out of 124 patients when compared to those who did not give history of HL. The P value is 0. 0061 and significant.^(16,17) Moscicki RA et al found antibodies against specific inner ear structures using immunofluorescence. The evaluation of patients when suspected should include thorough history taking, physical examination and an audiogram. Exclusion of other causes of hearing loss is necessary.

There is limited evidence to support pathophysiology of viral and vascular injuries to inner ear; the strongest evidence of pathophysiology is that of AIED. Endolymphatic sac is a critical organ in processing and modulating immunity in the inner ear. As a result of unidentified trigger due to antibody cross reactivity, viral injury or trauma, systemic lymphocytes are exposed to the systemic cochlear proteins. T immune cells of the circulation invade the blood labyrinthine barrier to reach the Endolymphatic sac. The initial site of entry of lymphocytes into the inner ear is the spiral modiolar vein adjacent to scala tympani-15, and thus the helper T cells are activated against the sensory and supporting cells within the cochlea. These infiltrating cells into Endolymphatic sac express IL-1 α , IL-2, TNF- α and NF- κ B necessary for initiation, modulation and amplification of the immune response. An extracellular matrix protein highly and specifically found in the inner ear called as cochlin is an antigen found to produce increased production of IFN- γ and cochlear inflammation in experimental animals. Hence these studies give evidence of an adaptive immune response against inner ear specific target antigen with AIED. In animal models, type II antigen antibody reaction or immune complexmediated damage (Type III) due to circulating antibodies against inner ear antigen are implicated in

the pathogenesis of hearing loss. Targets of these antibodies are stria vascularis, fibrocytes of the spiral ligament and supporting cells. The authors add that the AIED occurs usually in 3rd to 6th decade.

It may present unilaterally or bilaterally progressing over weeks to moths, which itself is a proof to the diagnosis. Even though the patients show unilateral involvement, but when measured accurately on audiometry may show asymmetric involvement on both sides. Fluctuating hearing loss is also common but overall course is progressive deterioration of hearing function. In the present study patients showed statistical significant correlation between impedance audiometry values and their incidence; patients with SLE (P value 0.040), Psoriasis (P value 0.004), Dermatomyositis (P value 0.015) and Vitiligo (P value 0.002).¹⁸

Yen YC, Lin YS, Weng SF et al in their study testing the hypothesis that Psoriasis patients have a risk to develop SSNHL found after 6 years of follow up; an 1. 51 times higher incidence than in the control group. They also concluded that associated hypertension is a co-morbid risk factor.⁽¹⁹⁾ Alopecia Areata occurs equally in both the sexes. The Incidence reported is 1–0. 2% with a lifetime risk of 1. 7%. (Safavi et al., 1995). One of the most possible etiologies is autoimmunity (McDonagh and Tazi-Ahnini, 2002 and Hordinsky and Ericson, 2004). This is supported by the coincidence of AA with other autoimmune disorders like morphea, Lichen Planus, Vitiligo, atopic dermatitis, Hashimoto's thyroiditis, (Brenner, 1979). More recently, it has been reported that there is a high prevalence of mood, adjustment, depressive and anxiety disorders in patients with AA (Ruiz-Doblado et al., 2003).⁽¹²⁾ Animal model studies corroborate the concept of Ti cell mediated autoimmune disease and different steps and aspects of the pathogenesis have been elucidated (Freyschmidt-Paul et al., 2004).⁽¹³⁾ Animal models have also suggested a role of vitamin A in the regulation of both the hair cycle and immune response to alter the progression of AA. (Duncan et al., 2013).⁽¹⁹⁾ Ucak H, Soylu E, et al I their study of 51 patients of AA found that SNHL was seen more frequently in patients with AA than the control group P-value < 0.002 at higher frequencies.

They concluded that follicular melanocytes may be important target cells in AA and it may have an effect on hearing function by affecting the melanocytes in the inner ear.⁽²⁰⁾ Sperling NM, Tehrani K, Liebling A, Ginzler E. et al evaluated patients aged below 65 years with SLE for aural symptoms and found that the patients gave combination of unilateral HL with or without tinnitus. There was statistical significance when compared with creatinine and C3 levels. Abnormal pure tone thresholds were seen in 7 out of 10patients. They concluded that aural symptoms are prevalent in SLE patients and asymmetric symptom and hearing loss is common. This may be related to immune complex disease and vasculitis seen in SLE.⁽²¹⁾ Bowman CA; Linthicum FH; et al prospectively studied patients with SLE and suggested a possible association between SLE and SNHL. They found in their patients 8% incidence of substantial, previously undetected HL without an attributed cause. They suggested that the physicians treating SLE should evaluate their patients for HL whenever there are aural symptoms.

They found association of Atopic Dermatitis with AA in maximum frequency with an O/E ratio of 2. 5, indicating two to three times more common in patients with alopecia areata. They also found thyroid disorders especially hypothyroidism with on O/E ratio of 3.2 in association with AA.⁽²²⁾ on investigation of Hearing and Outer Hair Cell Function of Cochlea in Patients with Psoriasis, Hayriye Karabulut, Ayse Serap Karadag, et al found no statistically significant difference between pure-tone thresholds of the patients and controls at all frequencies (p > 0.05).⁽²³⁾ Ozlem Karabudak, Rifat Eralp Ulusoy, et al Evaluated serologically the patients with psoriasis and found that mean platelet volume,

J of Evolution of Med and Dent Sci/eISSN-2278-4802, pISSN-2278-4748/Vol. 4/Issue 30/Apr 13, 2015 Page 5133

C-reactive protein and ceruloplasmin levels, were significantly increased, in the study group when compared to the control group.

The patients showed decreased antithrombin III and total homocysteine levels. Recent studies have revealed a hypercoagulable state in patients with an inflammatory disease which becomes a risk factor for atherosclerosis and thrombosis, and may interfere with the coagulation system, causing direct endothelial injury followed by facilitated thrombosis, and causing oxidative damage to the endothelium. The authors postulated that this may cause damage to the hair cells of the cochlea.⁽²⁴⁾ Juan C Amor-Dorado, Maria C Arias-Nunez, et al aimed to study evidence of hearing levels in their study to assess Audiovestibular involvement in patients with limited scleroderma (lssc), they evaluated a series of 35 consecutive patients fulfilling the criteria for lssc and had antibodies against centromere protein-B (CENP-B). Majority were females (94%). 77% of the patients showed hearing abnormality when compared to the control group (26%) with a P-value <0.001.

Audiometric tests pure tone average and speech reception threshold yielded significant differences between the control group and the patients with lssc. Abnormal oculocephalic responses were also noted which were statistically significant. Caloric tests were abnormal in 31% of the patients. They concluded that there is a strong evidence for inner ear compromise in patients with 1SSc.⁽²⁵⁾ Nikpour M, Stevens WM, Herrick AL, Proudman SM et al in their study of Epidemiology of systemic sclerosis, concluded that Systemic sclerosis is an autoimmune disease with multi-system involvement. Mainly two types; limited and diffuse with different course and prognosis. The incidence is on the rise mainly due to improved diagnosis and early detection is possible before skin involvement. Organic solvents and silica are the extensively studied environmental associations but no single risk factor has emerged. Genetic studies recently have shown human leukocyte antigen (HLA) haplotypes and polymorphisms as new susceptible factors. Some predictors of organ involvement and outcomes are identified.

Patients with Psoriatic arthritis and control population came to conclude that, compared to controls (8.3%, p < 0.001). Patients with PsA exhibited abnormal vestibular tests. Hearing loss of more than 30 dB affecting at least 3 contiguous frequencies over a period of 72 hours is defined as sudden Sensorineural Deafness.⁽²⁶⁾ Epidermolysis Bullosa is an autoimmune disease characterized by trauma-induced, sub epidermal blistering with no family history of the disease. Direct immunofluorescence shows immunoglobulin G deposited at the dermo-epidermal junction. Also anti-BM antibodies react with the BM matrix protein and type VII collagen, differentiating it from all other primary blistering diseases. The finding of ABMs to C-VII in SLE and BSLE, evidence that EBA and BSLE share an immunogenetic predisposition to C-VII autoimmunity, and an apparent association between susceptibility to SLE and EBA suggest a close relationship between SLE and autoimmunity to C-VII.⁽²⁷⁾

Involvement of Ear in SLE is reported by many authors but the mechanism and frequency of involvement is not well documented. Ioannis Kastanioudakis, Nausica Ziavra et al in their clinical study concluded that 1/4th of SLE patients in their study had SNHL in mid and high frequencies and this was a lower percentage when compared to other authors.⁽²⁸⁾ Roverano S, Cassano G, et al in a clinical study to evaluate SNHL in SLE patients found that 70% of the patients had HL and 66% had sensory neural loss at higher frequency bilateral and symmetrical. No correlation was found between SLE activity and hearing loss. They concluded that clinical evaluation of hearing thresholds will help

in SLE patients to assess the hearing function.⁽²⁹⁾ Seong Ho Cho, Haimei Chen, et al studied the association of the 4g/5g polymorphism of plasminogen activator inhibitor-1 gene with sudden sensorineural hearing loss. The 5 G/5 G genotype of PAI-1 polymorphism is linked to decreased plasminogen activator inhibitor-1 (PAI-1) levels and it has been suggested that lower PAI-1 levels may provide protective effects on inflammation, local microcirculatory disturbance, and fibrotic changes, which are likely associated with development of sudden sensorineural hearing loss (SSNHL). The minimum stimulus level that results in an observable decrease in acoustic admittance is defined as the acoustic reflex threshold. Acoustic reflex thresholds are usually measured from 500-2000 Hz, in both ipsilateral and contralateral modes, for each ear.

CONCLUSIONS: Autoimmunity is recognized as an etiological factor in the causation of SSNHL and SNHL. Similarly there are skin diseases with an etiology of autoimmunity. Autoimmunity is a disease with multiple facets in the pathogenesis making the immune system to react to body's normal tissue, which may include one or multiple organs. The present study showed statistical significance in the incidence of hearing loss by pure tone and impedance measurements in patients diagnosed with common autoimmune skin diseases. The P value being less than 0.05 in all the disease selected except Alopecia Areata. Hence it should be mandatory to evaluate clinical and audiological methods, all the patients with autoimmune skin diseases for early diagnosis and management.

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> Date of Submission: 18/03/2015. Date of Peer Review: 19/03/2015. Date of Acceptance: 31/03/2015. Date of Publishing: 10/04/2015.