Audiological and Electrophysiological Changes in Patients with Vitiligo

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Abstract The study was conducted to evaluate the audiological and electrophysiological findings in patients with Vitiligo and to compare the findings with otologically and audiological normal controls. Study group included 50 subjects (25 Males, 25 Females) with Vitiligo (Mean age-27.4 years) and control group contained 40 age-matched normal hearing subjects. Pure tone audiometry (PTA) with extended high frequency audiometry, Otoacoustic emissions (OAEs), Tympanometry, Auditory brainstem responses (ABR) and Middle latency responses (MLR) were conducted in all subjects. Comparison of the study group with the control group showed statistically significant differences ($p < 0.05$) on PTA, in Transient otoacoustic emissions (TOAEs) at 1, 2, 3, 4 kHz and in distortion product otoacoustic emissions (DPOAEs) at 357, 499, 704, 1003 Hz. On ABR, statistically significant differences were observed between the groups in wave I ($p < 0.01$) in both ears, wave V ($p < 0.05$) in left ear and on interpeak latency of I–III ($p < 0.01$, $p < 0.05$), III–V ($p < 0.01$ in left ear) and I–V ($p < 0.01$, $p < 0.05$) in left and right ears respectively. When patients with localized

vitiligo were compared with generalized vitiligo, the SNR of TOAEs was highly significant in both ears at 2 KHz ($p < 0.05$), 3 kHz ($p < 0.01$) and 4 kHz ($p < 0.05$). PTA average of 2 KHz, 4 and 8 kHz (PTA2) showed a significant difference ($p < 0.01$) when localized vitiligo was compared to generalized vitiligo. Results support possible auditory and electrophysiological changes in Vitiligo patients along with decreased cochlear function.

Keywords Vitiligo · ABR · MLR · OAEs · Pure tone audiometry · Melanocytes

Introduction

Vitiligo is an idiopathic disease that causes destruction of melanocytes in the skin, mucous membranes, eyes, inner ear, leptomeninges and hair bulbs [1, 2]. Various recent clinical and animal experimental studies [3–5] support the premise that the pathogenetic mechanisms of Vitiligo could be systemic events as vitiligo is associated with ocular [6–9] and auditory abnormalities and other autoimmune disorders [2, 3, 9, 10]. There have been few studies in India on the ocular and otic abnormalities and the presence of other autoimmune disorders in association with vitiligo [11–13].

While classifying vitiligo, the most widely used classification is localized, generalized, and universal types which are based on the distribution as explained by Groysman [14].

Localized vitiligo consists of focal, segmental and mucosal vitiligo. Focal vitiligo which has one or more macules in one area. Segmental vitiligo is characterized by one or more macules in a dermatomal or quasidermatomal pattern and most commonly occurs in children. More than half the patients with segmental vitiligo have patches of white hair or poliosis. This type of vitiligo is not associated

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with thyroid or other autoimmune disorders. Mucosal vitiligo affects mucous membranes alone.

Generalized vitiligo consists of acrofacial, vulgaris and mixed vitiligo. Acrofacial vitiligo occurs mainly on the distal fingers and periorificial areas. Vulgaris type has widely distributed scattered patches. Mixed vitiligo is a combination of any of the two, out of acrofacial, vulgaris or segmental vitiligo.

Universal vitiligo has complete or nearly complete depigmentation. It is often associated with multiple endocrinopathy syndromes.

It has been quoted earlier that vitiligo is predisposed to cochlear dysfunction and patients also have a high frequency hearing loss. In the present study middle latency responses (MLR) were also conducted along with peripheral auditory lesion test to find whether some changes occur in sub-cortical levels.

Aim

The present study aimed at evaluating the audiological and status of patients with vitiligo and also to compare the findings with otologically and audiotologically normal controls. The other aim was to study the effect of duration and type of vitiligo on the audiological status.

Materials and Methods

The study was conducted in Speech and Hearing Unit, Department of Otolaryngology, PGIMER Chandigarh. The study group included 50 patients (25 Males, 25 Females) with vitiligo attending out-patient Department of Dermatology in PGIMER. The age range varied from 11 to 50 years with a mean age of 27.4 years. In the study group, 16 patients were diagnosed as localized vitiligo and 34 as generalized vitiligo by dermatologist. While dividing as per the duration of vitiligo, 23 subjects had the duration of less than 60 months and 27 had more than 60 months. Subjects with a previous history of otologic disease, systemic diseases, neurologic disease, vascular disease, metabolic problems, ototoxic drugs used in the past, abnormal otoscopic findings and middle ear problems were excluded from the study. Control group contained 40 age and sex matched otologically and audiotologically normal subjects.

Consents were taken from the patients for enrollment in the research study. Detailed history was taken from the patient who included family history of vitiligo, type, site and duration of pigmentary disease. After a physical examination that included a complete Oto-rhino-laryngological examination, detailed audiological assessment was

done for all the patients by same audiologist. Audiological evaluation included:

1. Pure tone audiometry (PTA)
2. High frequency audiometry
3. Otoacoustic emissions (OAEs)—Distortion product OAEs (DPOAEs) and transient evoked OAEs (TOAEs)
4. Tympanometry
5. Auditory brainstem response audiometry (ABR)
6. Middle latency responses (MLR)

The audiological assessment was carried out in the sound treated rooms which conformed to American National Standards Institute ANSI S3.1 [15] and International Organization for standardization (ISO) standards for maximum permissible noise level. PTA was carried out using Madsen ORBITER 922 (Denmark) audiometer with TDH39 headphones and Sennheiser HDA200 headphones were used for high frequency audiometry. Hearing range of 0–20 dB HL at 0.25, 0.5 & 1 kHz (PTA1), 0–25 dB HL at 2, 4 & 8 kHz (PTA2) and 0–30 dB HL at 10, 12, 14 & 16 kHz (PTA3) was considered normal. Siemens SD 30 tympanometer was used for tympanometry and acoustic reflex testing. For tympanometry, the 226 Hz probe tone was used and the pressure was varied from +200 to –300 da pa. Type-‘A’ tympanogram was considered as normal and patients having any other type were excluded from the study. OAEs, ABR, and MLR were carried out by the systems developed by Intelligent Hearing System, (Miami, Florida, USA). TOAEs were performed with a wide band click in continuous mode and with an intensity of 90 dB SPL. For measuring DP gram, the frequency ratio of the primaries was $f_2/f_1 = 1.22$, with L1 and L2, set to 65 and 55 dB SPL respectively. For all the tests, normative established in the department were used as standards. Parameters considered in the TOAEs test were 1) signal-to-noise (SNR) ratio > 3 dB in at least three consecutive frequencies tested (1, 1.5, 2, 3 and 4 kHz). Parameters considered in the DPOAE test were 1) SNR ratio > 3 dB in at least three consecutive frequencies tested and amplitude of the signal in the 90th percentile of the normal distribution for the frequencies tested (357, 499, 704, 1003, 1409, 2000, 2822, 3991 and 5649 Hz) with reproducibility equal to or over 70 %.

ABR and MLR were measured in all subjects in the supine position with eyes closed. Insert earphones ER-3A (Intelligent Hearing System) were used to present stimuli. Silver-silver chloride button electrodes were used. The non-inverting electrode was placed at the vertex (Cz), inverting electrode was placed on either mastoid (M1, M2) and the ground electrode was placed on the forehead (Fz), using conduction gel. Impedance was kept below 3 KΩ. The peaks identified during ABR were- I, III, and V. The

absolute latencies of waves I, III, and V, and the inter-peak latencies of wave I–III, III–V and I–V were calculated. The normalcy criterion is as follows: Inter-peak Latency of wave I–III is 2.0 ± 0.4 ms, wave III–V is 1.8 ± 0.4 ms and wave I–V is 3.8 ± 0.4 ms. Waveforms were recorded at sound intensity of 90 dB n HL with alternating polarity and responses were repeated to ensure reproducibility. In MLR, peaks Na, Pa and Nb were identified. MLR peaks Na and Pa amplitude were measured. Wave Na to Pa was taken as the amplitude of Na and wave Pa to wave Nb was taken as the amplitude of Pa. The criteria used for MLR waves abnormalities were: (a) Wave Na amplitude <0.50 μ V, (b) Wave Pa amplitude <0.50 μ V.

Statistical Analysis

Mean, standard deviation were used for data description for both study and control group. Student's *t* test was used to compare between two sample means. Results were considered significant if $p < 0.05$. Comparisons were done between the control group and study group (vitiligo as a whole). In the study group with-in group comparisons were made first by dividing vitiligo based on two types studied (localized and generalized) and then by dividing vitiligo based on duration (less than 60 months, more than 60 months).

Results

In the study group, the majority of the subjects had normal hearing (Right ear-49, Left ear-48) at low frequencies (PTA1). In PTA2 out of 100 ears, 3 ears had mild hearing loss and 4 had moderate hearing loss. However, hearing at extended high frequencies (PTA3) was affected in a large number of subjects (out of 100 ears, 16 ears had mild hearing loss, 30 ears had moderate hearing loss, 26 ears had severe hearing loss and 3 ears had profound hearing loss).

In the study group, the DPOAEs were absent in 12 (24 %) subjects and 14 (28 %) subjects in right and left ears respectively. The TOAEs were absent in 28 (56 %) and 25 (50 %) subjects in right and left ears respectively.

Table 1 depicts the comparison of study group ($n = 50$) and control group ($n = 40$) on PTA. Statistically significant difference was found between Study and Control group for PTA1 in left ear ($p < 0.05$) and PTA2 & PTA3 in both right and left ears ($p < 0.001$).

Table 2 compares the study and control group on TEOAEs. SNRs were statistically reduced in the study group in left ear at 1, 3 & 4 kHz and in right ear at 1, 2, 3 & 4 kHz frequencies.

Table 3 shows the comparison of groups on DPOAEs. Almost all frequencies showed statistically lower SNRs in the study group.

Table 4 shows the comparison of study group and control group on ABR peaks and inter-peak latencies. Statistical significant differences were observed between the groups in wave I, wave V (left ear only), Interpeak latency I–III, III–V (left ear only) and I–V. No statistical differences were found in MLR latency and amplitudes between study group and control group.

The study Group was further divided into localized and generalized Vitiligo. Table 5 compares the group of localized vitiligo ($n = 16$) with generalized vitiligo ($n = 34$) on TOAEs,

Statistically significant differences in SNR values of the two groups were found in SNR at 2, 3 kHz ($p < 0.01$) and 4 kHz ($p < 0.05$) in the left and right ear respectively.

Statistically higher PTA2 ($p < 0.01$) was seen in generalized vitiligo as compared to localized vitiligo. Statistical significant difference was observed for the latency of wave Na ($p < 0.05$) in right ear. No significant of type was found between two groups on DPOAEs and ABR in both ears.

To study the effect of duration of Vitiligo, data of study group was further divided into two groups [Group 1: Vitiligo for 0–60 months ($n = 23$), Group 2: more than 60 months ($n = 27$)]. There was a significant difference ($p < 0.001$) in the means of the two groups revealing higher values with longer duration of vitiligo at 2, 4 and 8 kHz on PTA2. Additionally, there was an overall decrease in amplitude in all patients of vitiligo at all frequencies but significant difference between the two groups was observed at 499 Hz on DPOAEs.

No significant effect of duration was observed on TOAEs, ABR and MLR in both ears.

Discussion

The study has been carried out with the aim of finding whether the vitiligo has an effect on the hearing mechanism for which an audiological test battery has been conducted.

In patients with vitiligo, we found a significant hearing loss especially at high and extended high frequencies. This result can be due to the destruction of melanocytes in the inner ear which have multiple roles critical for hair cell survival, including maintenance of the normal function of the stria vascularis and the cochlea, the development of endocochlear potentials and ion and fluid gradient between the endolymph and perilymph. In studies on this theme, the evaluation of hearing revealed similar results, i.e., decreased hearing at high frequencies [16–18]. Ardiç et al.

Table 1 Comparison of study group and control group on pure tone audiometry

Pure tone average (in dB HL)		Study group (n = 50)		Control group (n = 40)		t value
		Mean	SD	Mean	SD	
PTA 1	Right ear	9.300	5.304	10.58	3.125	1.429
	Left ear	12.83	4.929	10.50	4.836	2.255*
PTA 2	Right ear	15.80	11.892	8.917	5.756	3.600**
	Left ear	15.30	10.021	9.042	6.370	3.600**
PTA 3	Right ear	46.600	20.165	24.281	4.140	7.628**
	Left ear	46.050	20.877	21.313	2.079	8.327**

* $p < 0.05$, ** $p < 0.01$ **Table 2** Comparison of study and control group on transient otoacoustic emissions (TEOAEs) testing

Frequency (Hz)	Ear	Study group		Control group		t value
		Mean (dB SPL)	SD	Mean (dB SPL)	SD	
1 k	R	1.47	2.69	2.69	2.07	2.27*
	L	1.52	1.33	5.22	4.32	5.18***
1.5 k	R	2.00	2.98	3.35	3.14	1.97
	L	2.31	3.22	4.05	4.99	1.86
2 K	R	1.32	4.17	4.11	4.59	2.85**
	L	1.75	4.83	3.84	4.49	1.64
3 K	R	1.63	3.25	3.95	4.07	2.83**
	L	2.76	3.71	6.52	4.66	4.00***
4 K	R	1.22	2.54	3.26	5.90	2.27*
	L	1.57	2.98	6.21	3.04	6.91***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ **Table 3** Comparison of study and control group on distortion product otoacoustic emissions (DPOAEs) testing

Frequency (Hz)	Ear	Study group		Control group		t value
		Mean (dB SPL)	SD	Mean (dB SPL)	SD	
357	R	2.41	3.83	4.71	2.91	3.04*
	L	2.68	5.59	9.00	4.45	5.60**
499	R	0.58	6.54	5.18	3.25	4.99**
	L	1.10	5.26	8.15	2.74	7.52**
704	R	0.52	4.80	6.48	3.94	6.07**
	L	1.28	6.48	8.32	2.82	7.53**
1003	R	1.95	5.92	8.35	4.45	5.48**
	L	1.88	3.58	8.12	3.67	7.72**

* $p < 0.01$, ** $p < 0.001$

[18] explained that Vitiligo seems to be an effective factor in hearing loss and that the mechanism for this condition might be absence of the preventive function of melanocytes in the inner ear. Tosti et al. [19] found hearing loss in 16 % of subjects with Vitiligo; they raised the hypothesis that part of the melanocytes was injured by auto-immunity due to Vitiligo.

OAEs are low intensity acoustic signals emitted by healthy cochlea. OAE recording is a reliable method to check the functionality of the hair cells in the cochlea. In the present study patients with vitiligo had remarkably reduced SNR of DPOAEs and TOAEs as compared to the control group. Angrisani et al. [20] reported that 66.7 % of their vitiligo patients (n = 21) had no OAEs, suggesting

Table 4 Comparison of study group (Group-I) and control group (Group-II) on ABR latencies

ABR latency (ms)	Ear	Study group (n = 50)		Control group (n = 40)		t values
		Mean	SD	Mean	SD	
Wave-I	R	1.64	0.15	1.56	0.06	3.630**
	L	1.65	0.16	1.54	0.06	4.558**
Wave-III	R	3.70	0.15	3.71	0.15	0.286
	L	3.67	0.22	3.67	0.146	0.057
Wave-V	R	5.52	0.26	5.55	0.13	0.286
	L	5.46	0.26	5.55	0.16	2.150*
Interpeak I–III	R	2.06	0.20	2.15	0.15	2.563*
	L	2.05	0.19	2.13	0.14	2.335*
Interpeak III–V	R	1.82	0.22	1.85	0.16	0.683
	L	1.75	0.26	1.89	0.12	3.145*
Interpeak I–V	R	3.87	0.31	4.00	0.12	2.610*
	L	3.81	0.26	4.02	0.15	4.831**

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ **Table 5** Comparison of two groups (Group 1-localized, Group 2-generalized) on TeOAEs

Frequency (Hz)	Ear	Group I		Group II		t value
		Mean (dB SPL)	SD	Mean (dB SPL)	SD	
1 k	R	1.57	2.12	1.51	2.11	1.27
	L	1.51	1.33	1.50	2.30	1.15
1.5 k	R	2.12	2.75	2.10	2.14	1.17
	L	2.11	2.72	2.10	2.25	1.15
2 K	R	1.53	3.95	1.40	3.56	2.05*
	L	1.65	3.83	1.51	3.89	2.04*
3 K	R	1.85	3.16	1.59	3.07	2.83**
	L	1.87	3.11	1.57	3.56	2.91**
4 K	R	1.42	2.49	1.30	2.51	2.02*
	L	1.62	2.85	1.49	2.66	2.03*

* $p < 0.05$, ** $p < 0.01$

cochlear dysfunction. Our study strengthens the hypothesis that Vitiligo is a significant factor for the altered cochlear function, and that melanin may, in fact, have an important role in cell metabolism, facilitating substance exchanges and maintaining endolymph, perilymph and ionic balance [21].

The present study found a significant difference between groups during ABR testing. Wave I is obtained from the distal end of the auditory nerve, near cochlea and altered cochlear function is usually seen in patients with Vitiligo. In contrast, Nikiforidis et al. [22] found a decrease in peak I latency and prolonged I–III interpeak latency while studying 30 patients with Vitiligo in comparison to the control group. Aydogan et al. [23] reported a statistically significant increase in the peak III latency and interpeak latency I–III in both ears and a significant increase in the peak V latency in the right ear as compared to controls.

Increase in Peak III latency and prolongation of I–II interpeak latency is also reported by Mahdi et al. [24].

MLR did not show any significant difference between the control group and study group in latency and amplitudes in the present study.

We also did an effort to see the effect of type and duration of vitiligo on auditory function.

Type of Vitiligo: A statistical significant difference was found in SNR of TOAEs in two groups (Group 1-localized, Group 2-generalized) in the left ear at 2, 3 & 4 kHz. This indicates decreased cochlear function near the basal end in patients with generalized vitiligo. But there is a dearth of research done to find differences in different types of vitiligo and correlation with outer hair cell dysfunction. Comparison of MLR latencies showed increased latency of wave Na in patients with generalized vitiligo. This indicates changes in the sub-cortical areas with an increase in

the extent of vitiligo. These findings need to be explored further.

Duration of Vitiligo

When the groups were compared on the basis of duration, significant differences were observed between the two groups in PTA2, with long term vitiligo patients having poorer hearing thresholds. The significant relation was also put forward by Aslan [17]. Schrott and Spoendlin [25] stated that hypopigmentation disorders for a long duration may lead to degeneration of the outer hair cells beginning at the basal turn of the cochlea while inner hair cells remain structurally and functionally intact. However, Shalaby et al. [26] found no relation between duration, severity of the disease (number of affected sites) and any audiological parameters. The finding should be further explored to implement these findings in clinical practice.

In the present study, there was no statistical significant difference found in the results of ABR with respect to the type and duration of vitiligo.

Conclusion

Vitiligo being a systemic disease showed positive involvement of cochlear structures. Accordingly, patients with Vitiligo can be evaluated with a battery of audiological tests. In general, patients with Vitiligo have a high frequency hearing loss of cochlear origin that was evident from the results of OAEs and may further involve higher auditory centers with an increase in the extent of the problem. The results should be studied on a larger sample and correlated further.

Limitation

The study group included localized and generalized vitiligo only in the present work. Patients with universal vitiligo could not be included due to rare availability.

Key Message/Recommendations

Extended high frequency audiometry should be done as it has an advantage in detecting early minute affection in the auditory sensitivity. Auditory function of patients with vitiligo should be regularly evaluated for early detection and monitoring. Use of protective measures in a noisy environment should be encouraged.

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Compliance with Ethical Standards

Ethical Standards All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Conflict of interest No conflict of interest as no funding was received from any agency. Richa Arya, Sanjay Munjal, Naresh Kumar Panda and Davinder Prasad declares that he/she has no conflict of interest.

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