The Effect of Otic Melanocyte Destruction on Auditory and Vestibular Function: a Study on Vitiligo Patients

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Abstract- The hallmark of vitiligo is the disappearance of melanocytes from the skin. As a result, of melanocytes presence in the auditory and vestibular apparatus, the involvement of these systems in vitiligo which targets the melanocytes of the whole body is possible; suggesting that vitiligo is a systemic disease rather than a purely cutaneous problem. A total of 21 patients with vitiligo were enrolled in this study. A group of 20 healthy subjects served as a control group. Pure tone audiometry (PTA), auditory brainstem responses (ABR) and vestibular evoked myogenic potentials (VEMP) were carried out in all participants. High frequency sensory neural hearing loss was seen in 8 (38.09%) patients. ABR analysis revealed 10 (47.61%) had an abnormal increase in latency of wave III, and 6 (28.57%) had an abnormal prolongation of IPL I-III, however, regarding our VEMP findings, there were no recorded responses on left ear of 1 (4.76%) patient and latency of p13 was prolonged in 5(23.80%) patients. There was no correlation between ages, duration of disease, and any of the recorded parameters (P>0.05). In the present survey, we highlighted the auditory and vestibular involvement in vitiligo patients.

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Introduction

Vitiligo (leukoderma) is an acquired, sometimes familial depigmentary disorder which results from selective destruction of melanocytes and characterized by pearl-white patches of diverse shapes and sizes, in the midst of normally pigmented skin (1-3).

It affects all races and has no sex prevalence. It has a worldwide occurrence of 0.3–1 % (4).

In Iran, there is no accurate published data; however, 0.9–1.2 % of the total population has been estimated to be suffering from vitiligo (5).

As a clinical classification of vitiligo, 7 types have been delineated, 1) generalized, 2) focal, 3) segmental, 4) acrofacial, 5) total, 6) inflammatory and 7) occupational (6).

Under the evolutionary viewpoint, the embryonic origin of human melanocytes are from the neural crest, and they are located in the epidermis, hair bulbs of the skin, the uveal tract, retinal pigment epithelium of the eyes, leptomeninges, and the inner ear (4,7). The presence of otic melanocytes was described by Alphonse Corti (1831) at first (3), and these cells are primarily localized throughout the stria vascularis and modiolus of the cochlea, but they also exist in the vestibular organs (7,8). Melanocytes may have an important role in the inner ear since hearing is affected in systemic disorders that affect pigmented areas such as the Vogt-Koyanagi and Waardenburg syndromes (3). The presence of melanocytes is not limited to the peripheral auditory system, abnormalities in the brainstem were found in both animals and humans with pigment disorders; additionally, neurons in the medial superior olivary nucleus of albino rabbits were shown to be 24% smaller than normal animals, and the branching density of its dendrites was significantly reduced (9), so melanocytes are also present in the central auditory system.

During the recent years, VEMPs have been used to

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detect vestibular damage. The method was initially described by Colebatatch and Halmagyi in 1992 as click evoked myogenic potentials (10). The presumed pathways of this vestibulocollic reflex start in the saccule of the inner ear, continue through the inferior vestibular nerve to the vestibular nuclei, the vestibulospinal tracts, and the sternocleidomastoid muscle (SCM) (11). The saccule has not only anatomic proximity to the auditory system but also the great similarity between their hair cell ultrastructures, hence, assessing subclinical deterioration of the saccular neuroepithelium associated with vitiligo became self-evident. Evaluation of auditory function in patients with vitiligo has been the subject of some studies, and a variety of abnormalities was reported.

To the best of our knowledge, there was no reported study considering vestibular evaluation in these patients. In this regard, the present study was designed to apply conventional pure tone audiometry (PTA) and auditory brainstem responses (ABR) to detect any auditory involvement; furthermore, vestibular evoked myogenic potentials (VEMP) test was achieved in these patients.

Materials and Methods

Subjects

A case-control study was performed on 21 patients with vitiligo (12 females) attending a dermatology clinic in a university hospital center, from June 2010 to July 2011.

Patients all had a definitive diagnosis of vitiligo thorough medical history and clinical examination verified by a dermatologist.

Generalized, focal, segmental, acrofacial, total, inflammatory, and occupational vitiligo types were encountered in 12 (57.14%), 5 (23.81%), 3 (14.29%), 0(0%), 1 (4.76%), 0 (0%) and 0 (0%) patients, respectively.

A total of 21 age and sex matched healthy subjects (11 females), without any history of auditory and vestibular symptoms, participated as a control group.

The following exclusion criteria for both patient and control groups were applied to baseline history of familial hearing loss, oral ototoxic drug or corticosteroid intake, chronic noise exposure, head trauma, metabolic, neurological, vascular and autoimmune disease, any systemic disease such as diabetes or hypertension, age>46 years and contraindication for VEMP testing (e.g. cervical arthritis).

A questionnaire containing demographic data, disease onset as well as the history of auditory and vestibular problems was completed for each patient.

Pure tone audiometry

After otoscopic examination, participants underwent audiometric test using a Madsen Orbiter 922 diagnostic audiometer (Madsen Electronics, Denmark) at the frequencies of 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 KHz for air conduction and between 0.25 and 4.0 KHz for bone conduction. Pure Tone Averages (PTA) were calculated at frequencies of 0.5, 1 and 2 KHz; normalcy was based on the criteria of the American Speech-language-Hearing Association (ASHA, 1978) for a threshold below or equal to 20dBHL (12).

ABR

ABR was measured using ICS Charter device (GN Otometric, Denmark). Three electrodes were placed on the vertex (noninverted), the ipsilateral mastoid (inverted), and the contralateral mastoid (ground). Inter-electrode impedance was kept below 5kΩ. The acoustic stimuli were rarefaction clicks presented at a repetition rate of 13.1/sec, at an intensity of 80dB normal hearing level (nHL), with 0.1 ms duration that delivered monaurally to TDH 39 earphones. Responses to 2048 clicks were preamplified and bandpass between 100-3000 Hz. The analysis time of the screen was 10 ms. Duplicate recordings were made to check reproducibility. Absolute latency values of waves I, III and V and interpeak latencies (IPL) of I-III, III-V, and I-V, were compared with the results of the control group in each ear.

VEMP

Finally, all candidates underwent the VEMP testing with a clinical device of EPIC-Plus (LABAT, Italy). During recording, participants were in a sitting position with the head rotated away from the stimulated side to activate the ipsilateral SCM muscle. Muscle activation was monitored via feedback method. The surface electrodes were placed as follow: on the upper third of SCM as a noninverted electrode, the upper sternum as an inverted electrode, and on the forehead as a ground electrode. Tone burst of 500Hz was presented at a rate of 4.7/sec through an insert receiver. The stimuli intensity was 95dBnHL, and an electromyographic signal was amplified and bandpass filtered (10-2000 Hz). The analysis window was 100 ms. Responses to 150 sweeps were averaged, and the procedure was performed twice to ensure reproducibility. The latencies of the initial positively (p13) and subsequent negativity (n23) were analyzed; VEMP amplitudes corresponded to

the p13-n23 interpeak amplitude difference. The amplitude ratio (AR) index was calculated according to the formula (Ar-Al)/ (Ar+Al) * 100, in which Ar (Al) corresponds to stimulation of the right (left) ear.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences while all participants were requested to fill an informed consent.

Statistical analysis

SPSS software, version 11.5 (Chicago, IL, USA) was used for statistical evaluation.

To compare different values between study and control groups, non-parametric (Mann-Whitney U-test) test was used, since it can be more appropriate for small samples and when the normality assumption is not satisfied. The criterion for statistical significance was defined as *P* value≤0.05. Pearson's correlation was used to find a significant relation between two numeric variables.

Results

Mean (± standard deviation) of age was 30.14 (± 8.06) years (range, 19-44 years) for patients and 31.19 (± 7.93) years (range, 18-44 years) for controls. There was no statistically significant difference between these two groups according to sex and age (*P*>0.05).

The mean duration of disease was 9.62 ± 8.37 years (range, 0.5-30 years) and nine (42.85%) patients had a positive family history of the disease.

The results of the audiometric test are shown in (Table1). Thresholds of audiometry were statistically greater in both ears of patients at 2, 4, and 8 KHz (*P*≤0.05).

Table 1. Comparison of Pure tone audiometry results between patient and control groups.

	Patient group	Control group	
Ear/Frequency(Hz)	**Mean ± SD(dB)**	**Mean ± SD(dB)**	***P*-value**
R250	8.57±3.91	9.04±3.39	0.585
L250	9.05±4.36	10.01±4.47	0.632
Total	8.81±4.13	9.51±3.93	0.457
R500	8.33±2.41	7.23±3.56	0.140
L500	8.57±3.58	7.61±3.39	0.439
Total	8.45±2.99	7.42±3.47	0.141
R1000	8.10±3.34	7.14 ±2.98	0.388
L1000	7.86±4.05	7.93±2.93	0.599
Total	7.98±3.69	7.53±2.95	0.751
R2000	9.76±5.11	6.66±2.41	0.021
L2000	11.90±9.01	7.14±3.38	0.048
Total	10.83±7.06	6.90±2.89	0.018
R4000	17.14±12.50	8.57±4.22	0.005
L4000	14.76±10.89	8.09±4.02	0.028
Total	15.95±11.69	8.33±4.12	0.000
R8000	15.48±11.71	8.30±4.06	0.002
L8000	18.09±15.36	10.43± 4.74	0.042
Total	16.78±13.53	9.36±4.40	0.002
R PTA	8.73±2.16	7.22±2.75	0.058
L PTA	9.44±3.99	7.59±2.59	0.082
Total	9.08±3.07	7.40±2.67	

Abnormal pure tone thresholds were found in 8 (38.09%) patients including 5 patients with generalized, 1 with total and 2 with the segmental type of disease, of whom three had unilateral, and five had a bilateral sensory neural hearing loss.

Table 2 compares ABR findings of patients and controls. A statistically significant increase was found in absolute latency of the third peak in right and left ear of patients group (*P*=0.022 and *P*=0.001, respectively).

Of 21 patients, 10 (47.61%) had an abnormal increase in latency of wave III (greater than 2.5 standard deviations from the mean value in normal control subjects) and an abnormal increase in IPL of I-III was also detected in 6 (28.57%) patients; however, differences in other peak latencies and IPLs did not reach a statistically significant level. Increase in absolute latency of wave III without any changes in absolute latency of wave V, as expected, contributes to the

decrease in IPL III-V, a finding that was demonstrated in 2 (9.25%) patients.

When considering VEMP results (Table 3), the following was evidenced. There was an absent response on left ear of 1 (4.76%) patient, latency of p13 was significantly prolonged in left ear of our patients in comparison with control group (P=0.001), this prolongation was noted in 5(23.80%) patients (greater than 2.5 standard deviation of the mean value in normal control subjects). No differences for the latency of n23 and the absolute value of amplitude were noted (P>0.05). Since the normal value of AR is defined as ≤ 0.34, 1 (4.76%) patient had abnormal AR, however, it was not statistically meaningful (P=0.113), in general, 7(33.33%) patients had abnormalities in VEMP.

Table 2. Comparison of ABR parameters between patient and control groups.

Patient group(n=21)		Control group(n=21)	
Ear/Variable	**Mean±SD (ms)**	**Mean±SD (ms)**	***P*-value**
R/ I Latency	1.50±0.12	1.46±0.10	0.429
L/ I Latency	1.50±0.13	1.45±0.17	0.193
R/ III Latency	3.63±0.25	3.62±0.24	0.024
L/ III Latency	3.62±0.17	3.45±0.10	0.001
R/ V Latency	5.46±0.26	5.43 ±0.15	0.629
L/ V Latency	5.44±0.21	5.42±0.15	0.421
R/IPL I-III Latency	2.18±0.27	1.99±0.13	0.009
L/IPL I-III Latency	2.11±0.11	2.02±0.17	0.033
R/IPL III-V Latency	1.83±0.14	1.98±0.13	0.006
L/IPL III-V Latency	1.82±0.13	1.95±0.16	0.008
R/IPL I-V Latency	3.96±0.22	3.99±0.58	0.981
L/IPL I-V Latency	3.93±0.18	3.95±0.19	0.513

Table 3. Comparison of VEMP parameters between patient and control groups.

Patient group(n=21)		Control group(n=21)	
Ear/Variable	**Mean ± SD**	**Mean ± SD**	***P*-Value**
R/p13 latency(ms)	13.14±1.55	12.79±0.96	0.438
L/p13 latency(ms)	14.03±1.75	12.96±0.76	0.008
R/n23 latency(ms)	21.60±1.75	21.96±1.06	0.351
L/n23 latency(ms)	22.49±1.68	22.40±1.07	0.852
R/p13-n23 amplitude(µv)	73.97±30.16	75.62±21.08	0.880
L/p13-n23 amplitude(µv)	77.83±31.64	78.25±18.80	0.933
AR	0.14±0.11	0.09±0.15	0.117

Discussion

Although melanocyte loss in vitiligo is predominantly confined to the patient's skin, alterations in the extracutaneous sites have been reported and implied sometimes for the inner ear with an associated function compromise in this sensory organ (6). The exact functions of otic melanocytes are not known; they do not appear to be essential for normal hearing. These pigments are assumed to play a protective role against environmental damage (13). Murillo Cuesta *et al*., (13) stated that, compared to pigmented mice, albino mice show a higher prevalence of age-related hearing loss and poorer recovery of auditory thresholds after getting exposed to noise.

There are discrepancies in the literature about the

influence of vitiligo on auditory thresholds. Some authors state that vitiligo influences are hearing (3,4,8,9,14–17) whereas others question such influence (18–19).

The hearing loss pattern in present experiment was as follows: in 3 (14.28%) patients, loss was in the range of 2–8KHz; in 3 (14.28%) patients, it was limited to 4–8 KHz and in 2 (9.52%) patients, it was limited to 4 KHz only. However, pure tone average (PTA) of all patients was within the normal range. Current findings strengthened the hypothesis that an alteration of the inner ear pigment cells might favor the occurrence of hypoacusis.

Some studies were done, which dealt with ABR in patients with vitiligo. The sequences of peaks in the ABR recording reflect the synaptic activity of consecutive nuclei along the afferent in auditory pathway in the brainstem.

Abnormalities of ABR findings in the present study consisted of increased wave III latency and IPL I-III. Usually, wave III is associated with a neural activity that mainly originates from the superior olivary complex (SOC) within the brainstem. The increased IPL I-III was explained to be due to abnormal synaptic activity and transmission of the action potential from the auditory nerve to the lower brain stem (4,18). In accordance with present results Elsaied *et al*., (18) noted a statistically significant increase of the IPL I-III in patients as compared to the controls. Nevertheless, other investigators such as Aydoghan *et al*., (4) found statistically significant increase in both ears of the wave III latency and IPL I-III and a significant increase of the wave V latency in the right ear compared with the control; they explained that this finding might be a result of delayed synchronization of action potentials in brainstem nuclei. These results are in contrast to Shalaby *et al*., (19), who found no statistically significant difference between cases and controls in all ABR measured parameters and they recommended postmortem histopathological studies of the inner ear and brainstem to provide more accurate knowledge in vitiligo patients.

There was no correlation between ages, duration of disease and wave III and I-III IPL in left ear (P>0.05), the same results were confirmed by Elsaied *et al*., (18) and may be explained by that the affection of otic melanocytes occurs at the start of the vitiligo and then stabilized afterward.

No study has been encountered in the literature addressing vestibular manifestation in vitiligo patients. Regarding our VEMP findings, after exclusion of one ear with no recorded VEMP, the single abnormality index was the statistically significant prolongation of p13 on the left ear of our patients (P=0.001). Although the mechanism for this abnormality cannot be clearly indicated, it seem plausible that melanocytes take part in vestibular metabolism through the apparent relationship between the dark cells and the adjacent blood vessels; and in response to various stressful conditions, these cells have been reported to show increased melanin synthesis (20,21), additionally, as Wright *et al*., (22) provided evidence in their animal study, posterior-superior portion of the membranous wall of the saccule is lined by melanin and these pigmented cells play an active role in regulating endolymph composition which has an important role in modulating the vestibular stimuli; hence, one can deduce that the increase in latency of wave p13 may be due to the disturbance of stimuli transduction through inferior vestibular nerve.

The failure to evidence any amplitude abnormalities of VEMP in our survey might be due to the marked interindividual variability of amplitude in normal.

In summary, we have presented evidence implying that apart from established auditory involvement in vitiligo, as a result of auditory and vestibular adjustment, the vestibular system was likely affected by the similar condition; however, in our study, the auditory involvement is more prominent than the vestibular system.

We recommend that a larger study applying other vestibular tests such as video nistagmography (VNG) and computerized dynamic posturography (CDP) is needed for complete evaluation of the vestibular system in these patients.

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