

Assessment of audiovestibular system in patients with vitiligo: a case–control study

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Background

Vitiligo is characterized by loss of epidermal melanocytes. Alterations in melanocytes in extracutaneous sites have been reported in vitiligo and sometimes implied for the inner ear along with an associated compromise in function.

Aim

The aim of this study was to map the auditory and vestibular functions in patients with vitiligo.

Materials and methods

A total of 30 patients with vitiligo vulgaris and 30 age-matched and sex-matched healthy controls were enrolled in this study. Pure tone audiometry and measurements of auditory brainstem responses, cervical vestibular-evoked myogenic potential (cVEMP), and videonystagmography (VNG) were carried out in all participants.

Results

Mean hearing thresholds of patients with vitiligo were highly statistically significantly lowered at 4 and 8 kHz than the controls. Analysis of brainstem auditory-evoked potentials (BAEP) revealed statistically significantly prolonged wave III, wave V, and interpeaks of I–III and I–V latencies in both ears of 18 (60%) patients and in the left ear of two (6.6%) patients in the vitiligo group than the controls. VNG findings showed canal paresis in nine (30%) patients. There was a negative statistically significant correlation between disease duration and pure tone audiometry, BAEP, and latency of N23 of cVEMP.

Conclusion

This study sheds light on the importance of melanocytes for proper functioning of the auditory and vestibular system. The presence of high-frequency hearing loss, BAEP abnormalities, and cVEMP changes are valuable findings in patients with vitiligo. This highlights the importance of follow-up along the disease course for early detection of auditory abnormality. cVEMP testing can be used for the evaluation of the vestibulocolic reflex in patients with vitiligo. Moreover, VNG testing can be an important tool for assessment of the vestibular system in patients with vitiligo.

Keywords:

brainstem auditory-evoked potentials, cervical vestibular-evoked myogenic potential, hearing loss, vitiligo, videonystagmography

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Introduction

Vitiligo is an acquired depigmenting disorder resulting from selective destruction of melanocytes. It is characterized by milky-white patches of skin of different sizes and shapes [1].

Many possible causes of vitiligo have been proposed, including stress, infections, mutations, neural factors, melatonin receptor dysfunction, and impaired melanocyte migration and/or proliferation. In addition, the accumulation of toxic intermediate products of melanin synthesis [2].

Melanocytes are located in the epidermis, the hair bulbs of the skin, the uveal tract, the retinal pigmented

epithelium of the eyes, the leptomeninges, and the inner ear [3,4].

Alphonse Corti (1831) was the first researcher to mention the presence of pigment cells in the inner ear [3]. There are many melanocytes in the human cochlea, particularly in the modiolus, in the osseous spiral lamina, in Reissner's membrane, and in the vascular stria; melanocytes are found especially in

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highly vascularized areas of apparently important secretory or metabolic function [5].

The exact functions of otic melanocytes are not known. They do not appear to be essential for normal hearing but these pigments are assumed to play a protective role against environmental damage [6]. Melanin may also have a role in the vasomotor function in the inner ear [5,7].

There have been contradictory reports about the influence of vitiligo on auditory thresholds. Some authors state that vitiligo influences hearing [4,8–13], whereas others question such influence [14]. To the best of the author's knowledge, no previous reports investigated the vestibular function of the ear in patients with vitiligo.

Aim

The aim of this study was to investigate whether the presence of fewer melanocytes affects the auditory and vestibular functions in patients with vitiligo.

Materials and methods

The study was approved by the local research ethics committee of the Faculty of Medicine, Beni Suef University. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The purpose of the study was explained to each patient, and a written informed consent was taken before data collection. Patient confidentiality was maintained by code numbers given to each patient, and all personal data were concealed.

Selection of the study participants

In total, 30 patients with generalized vitiligo referred to the Dermatology Clinic at Beni Suef University Hospitals (Beni Suef, Egypt) and 30 age-matched and sex-matched healthy controls were examined at the auditory clinician in the period between March and August 2017.

Patients between 15 and 60 years with definitive diagnosis of generalized vitiligo were included in the study. Diagnosis of vitiligo was confirmed through clinical examination. The vitiligo surface area (%) was determined according to the rule of nine (divides the body into sections that represent 9% of the body surface area), and the vitiligo activity was assessed using the vitiligo disease activity score (a six-point scale for assessing disease activity;

ranging from +4, active in the past 4 weeks, to -1, spontaneous repigmentation of the vitiligo lesions) [15].

Exclusion criteria

The study excluded patients younger than 15 years and older than 60 years, a history of any middle ear disease, previous ear surgery, familial hearing loss, oral ototoxic drug or corticosteroid intake, chronic noise exposure, neurological, vascular, or autoimmune disease.

All participants who participated in this study were subjected to the following:

- (1) Full history taking.
- (2) Otological examination.
- (3) Audiological evaluation, which included tonal audiometry in the frequency range 0.25–8 kHz using orbiter 922 in a sound-treated room with a TDH 39 earphones. Speech audiometry was performed, including speech reception threshold using arabic spondee words [16], and word discrimination score, using arabic phonetically balanced words [17].
- (4) Immittanceometry was done using GSI 33 Grason-Stadler (USA), calibrated according to the ISO standards, using single-component, single-frequency tympanometry with a probe tone of 226 Hz. Testing of the acoustic reflex thresholds, for ipsilateral and contralateral elicited reflexes, was done using pure tones at 500, 1000, 2000, and 4000 Hz.
- (5) Brainstem auditory-evoked potentials (BAEPs) were performed using Interacoustic Eclipse (Denmark) 'EP15'. The reference electrodes were placed on the right (A2) and left (A1) mastoids; the active is on the scalp at the vertex (Fz position of the 10–20 International System of EEG electrode placement) and the ground electrode is on the lower midfrontal area (Fpz position). Ag/AgCl electrodes filled with conductive paste were fixed to the skin that was abraded with a skin preparation gel. Electrode impedances were less than 5 k Ω , and interelectrode impedances were less than 2 k Ω . Click was presented at a rate of 21.1 stimuli per second in rarefaction polarity at intensity of 80 dBHL. Averaged potentials to 1200 clicks were obtained. Two recordings were obtained to ensure the replicability of the waveforms. The latencies of waves I, III, and V and interpeak latencies of I–V, I–III, and III–V Interpeak Latencies (IPLs) were studied with BAEPs.

(6) Cervical vestibular-evoked myogenic potential (cVEMP) was performed using Interacoustic Eclipse 'EP15'. The surface electrodes were placed as follows: the active (positive) electrode, right then left, placed on both upper 2/3 of sternocleidomastoid muscles; the inverting (negative) electrode placed on the upper sternum (suprasternal notch); and the ground electrode placed on the forehead. Two repeatable recordings were obtained for each condition. Participants were given 30–60 s to relax between each recording to avoid fatigue. During recording, the subject is instructed to raise his head and tilt it away from the stimulated side throughout the test to ensure good muscle tone.

cVEMP responses were obtained by binaural acoustic stimulation and recorded from bilateral sternocleidomastoid muscles with short tone burst at frequency of 500 Hz of a rarefaction polarity. Intensity used is 95 dBHL. cVEMP response were judged as either present or absent according to the presence or absence of P13–N23 biphasic response. The latencies of peaks P13 and N23 (in ms) and P13–N23 peak to peak amplitude (in μ V) and interaural amplitude difference (IAAD) ratio were measured. The IAAD was evaluated as follows: $[(Ar-AI)/(Ar+AI) \times 100]$, where Ar indicates the P13/N23 peak to peak amplitude on the right side, AI that on the left side and (Ar-AI) the absolute value of (Ar-AI) [18,19].

(7) Vestibular system evaluation using videonystagmography (VNG) ICS Chart 200 included (a) normal eye movement function testing using a standardized battery of tests: (i) smooth pursuit testing at the 0.2–0.7 Hz in the horizontal plane, (ii) saccade testing with amplitudes ranging from 5° to 25°, (iii) spontaneous nystagmus testing while patients sitting in the upright position and looking forward both in dark and light conditions, and (iv) eccentric gaze testing; (b) positional and positioning testing; and (c) water caloric tests, in which, bithermal caloric tests were performed, and the ear was irrigated with water at temperatures of 30 and 44°C for 40 s. The recordings of responses were conducted for 3 min. Canal paresis and directional preponderance were calculated according to Jongkees' formula. Values greater than 20% for canal paresis and 25% for directional preponderance were considered abnormal [20].

Statistical methods

Data were coded and entered using the statistical package for the social sciences, version 24 (SPSS;

SPSS Inc., Chicago, Illinois, USA). Data were summarized using mean, SD, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the nonparametric χ^2 -test. Mann–Whitney test was used for comparing categorical data. Correlations between quantitative variables were done using Spearman's correlation coefficient. *P* values less than or equal to 0.05 were considered as statistically significant [21].

Results

This study included 30 patients with generalized vitiligo and 30 controls. The patients with vitiligo included six (20%) male patients and 24 (80%) female patients. Age of the patients ranged between 16 and 55 years, with a mean of 30.93 ± 12.55 years. A total of 30 healthy participants (control group) included 16 males and 14 females, whose age ranged from 16 to 39 years, with a mean of 26.40 ± 7.06 years.

There were no significant associations between the patient's sex and the hearing thresholds, except for the pure tone audiometry (PTA) at 250 Hz, where the females showed significantly higher mean value than males ($P=0.045$), and at 4 kHz, where the males showed higher mean value than females ($P=0.012$). There was no statistically significant difference between the patients and control groups regarding sex ($P=0.754$) or age ($P=0.233$).

Regarding the hearing function

Mean hearing thresholds were statistically significantly greater in both ears of patients with vitiligo at 0.25, 0.5, 1, 2, 4, and 8 kHz compared with controls ($P \leq 0.05$). Meanwhile, when we compared the right ear in cases with same ear in controls and the same was done for the left ear, we detected significant differences in most of the PTA thresholds (Table 1).

In the BAEP, cases showed significantly longer latencies of right wave III, right and left wave V, and interpeaks of right I–III and right and left I–V than controls. However, there was no statistically significant difference regarding BAEP wave I latency and interpeak III–V latency between both the groups (Table 2).

Regarding vestibular function

cVEMP was absent bilaterally in eight (26.6%) of 30 and absent unilaterally in six (20%) of 30 in the left ear. In the remaining 53.3% of patients with vitiligo, six of them showed normal cVEMP response and 10 (33.3%)

showed bilaterally preserved cVEMP response. P13 and N23 mean latencies were statistically significantly delayed in patients with vitiligo compared with controls. There was no statistically significant difference regarding the mean P13–N23 amplitudes between controls and patients with vitiligo. IAAD ratio was abnormal (prolonged) in 1/10 of patients with vitiligo (10%) and normal in 9/10 (90%) of patients. In 46.6%, IAAD could not be calculated (Table 3).

VNG results showed that nine (30%) patients with vitiligo had canal paresis: three (10%) of them had right canal paresis, six (20%) left canal paresis, and one (3%) bilateral canal paresis. Moreover, nine (30%) patients showed spontaneous nystagmus, one (3%) patient had abnormal saccadic testing, and one (3%) had abnormal smooth pursuit. Overall, eight (26.6%) patients of nine patients with vestibular affection showed peripheral vestibular manifestations and one (3%) showed central vestibular manifestations (Table 4).

Table 1 Mean hearing thresholds of patients with vitiligo and controls regarding pure tone average (dBHL) in the right and left ears

PTA	Control group		Vitiligo group		P value
	Mean	SD	Mean	SD	
250 Hz					
Right	16.33	3.99	20.66	4.95	0.013*
Left	16.33	4.42	19.66	4.80	0.058
500 Hz					
Right	16.66	3.08	20.33	5.81	0.040*
Left	18.33	3.62	22.00	5.60	0.042*
1 kHz					
Right	19.33	2.58	21.66	6.45	0.204
Left	17.66	3.19	21.66	5.87	0.028*
2 kHz					
Right	19.66	3.99	20.66	5.93	0.593
Left	18.00	4.55	23.00	7.02	0.028*
4 kHz					
Right	19.00	4.30	30.00	11.33	0.002*
Left	18.66	3.51	31.33	9.90	0.000*
8 kHz					
Right	19.66	3.99	35.33	12.74	0.000*
Left	20.33	2.28	37.66	11.78	0.000*

PTA, pure tone average; * $P < 0.05$, means significant.

Table 2 Comparison between vitiligo group and control group regarding brainstem auditory-evoked potentials results

BAEP latencies in ms	Control group		Vitiligo group		P value
	Mean	SD	mean	SD	
Wave I latency					
Right	1.37	0.16	1.35	0.14	0.825
Left	1.38	0.18	1.36	0.16	0.665
Wave III latency					
Right	3.42	0.17	3.57	0.23	0.005*
Left	3.46	0.23	3.63	0.25	0.066
Wave V latency					
Right	5.41	0.15	5.63	0.23	0.005*
Left	5.37	0.19	5.68	0.29	0.002*
I–III latency					
Right	2.11	0.23	2.22	0.28	0.007*
Left	2.09	0.24	2.27	0.28	0.072
III–V latency					
Right	1.94	0.23	2.05	0.13	0.110
Left	2.02	0.54	2.05	0.21	0.886
I–V latency					
Right	4.05	0.22	4.27	0.27	0.022*
Left	3.98	0.22	4.32	0.33	0.002*

BAEP, brainstem auditory-evoked potentials; * $P < 0.05$, means significant.

There was no statistically significant correlation between age, disease activity, extent of vitiligo and PTA, BAEP, and cVEMP findings. However, there was a negative statistically significant correlation between disease duration and PTA at 4 and 8 kHz, BAEP at waves III and V and interpeaks of I-III and I-V, and latency of N 23 of cVEMP (Table 5).

Discussion

Vitiligo is a relatively common disease that results in loss or reduction of melanocytes [22]. Melanocyte is an important cell to keep a normal function of cochlea and the stria vascularis and for hair cells as well [4,23]. Several studies report impaired hearing following disruption of melanin synthesis, melanosome structure, or their distribution [24].

In the present study, we found that the mean hearing thresholds of patients with vitiligo were significantly lower than the controls at 250 Hz, 1 kHz, and 2 kHz, and the difference was more marked at 4 and 8 kHz (Table 1).

These results were in accordance with Mahdi *et al.* [25], who found that patients with vitiligo had lowered hearing thresholds starting from 2 to

8 kHz compared with controls. This was explained by possible alteration of the inner ear pigment cells that lead to sensorineural hearing loss.

Similarly, Mohamed *et al.* [26] reported statistically significant lower hearing thresholds at frequencies 4, 8, and 10 kHz for the vitiligo group when compared with the control group.

In contrary to our results, Elsaied *et al.* [14] found no statistically significant difference between normal participants and patients with vitiligo regarding the hearing thresholds.

Hearing loss in patients with vitiligo is referred to the loss of inner ear melanocytes which play a role in keeping the normal function of the stria vascularis and the cochlea. Moreover, melanocytes are effective in development of endocochlear potentials and preservation of the gradient of ion and fluid between the endolymph and perilymph [27].

In the current study, the authors found statistically significant prolonged wave III, wave V, and interpeaks of I-III and I-V latencies of BAEP findings in both ears of 18 (60%) of 30 patients and in the left ear of two (6.6%) patients in the

Table 3 Comparison between vitiligo group and control group regarding cervical vestibular-evoked myogenic potential results

cVEMP parameters	Control group (n=30)		Vitiligo group (n=30)		P value
	Mean	SD	Mean	SD	
P13 latency in ms					
Right	13.91	0.82	15.41	0.92	0.000*
Left	14.03	1.21	15.23	1.30	0.027
N23 latency in ms					
Right	22.63	1.74	24.91	1.26	0.002*
Left	22.33	0.87	25.20	1.49	0.000*
P13-N23 amplitude (µV)					
Right	60.79	21.02	45.86	18.70	0.094
Left	64.62	27.22	47.17	13.53	0.074

cVEMP, cervical vestibular-evoked myogenic potential; * $P < 0.05$, means significant.

Table 4 Videonystagmography findings in vitiligo group and control group

VNG	Vitiligo group (n=30) [n (%)]	Control group (n=30) [n (%)]	P value
Spontaneous nystagmus	9 (30.0)	0.0 (0.0)	<0.001**
Pursuit test			
Normal	29 (96.6)	30 (100)	0.500
Abnormal	1 (3.3)	0.0 (0.0)	
Saccade test			
Normal	29 (96.6)	30 (100)	0.500
Abnormal	1 (3.3)	0.0 (0.0)	
Water caloric test			
Normal	21 (70.0)	0.0 (0.0)	<0.001**
CP	9 (30.0)	0.0 (0.0)	

CP, canal paresis; VNG, videonystagmography; ** $P < 0.05$, means significant.

vitiligo group compared with the control group (Table 2).

These results were similar to the results of Mahdi *et al.* [25], who reported that BAEP showed increased latencies of wave III and interpeak of I–III in vitiligo group when compared with

controls and Elsaied *et al.* [14] who reported a statistically significant delay in the left ear wave III latency and in interpeak I–III and interpeak I–V latencies. Moreover, a statistically significant delay was found in the right ear interpeak III–V in the patients with vitiligo compared with the control group.

Table 5 Correlation between disease extent (percentage), disease duration (months), vitiligo disease activity score, age (years), and estimated parameters among the vitiligo group

	Duration	VIDA	%	Age
PTA 250				
Pearson's correlation	0.288	−0.150	0.075	0.458
Significance (two-tailed)	0.122	0.428	0.693	0.112
PTA 500				
Pearson's correlation	0.173	−0.136	0.232	0.341
Significance (two-tailed)	0.361	0.475	0.217	0.065
PTA 1000				
Pearson's correlation	0.153	0.224	0.415	0.403
Significance (two-tailed)	0.421	0.234	0.123	0.271
PTA 2000				
Pearson's correlation	−0.011	0.202	0.358	0.417
Significance (two-tailed)	0.956	0.284	0.052	0.122
PTA 4000				
Pearson's correlation	−0.402*	0.177	0.022	0.228
Significance (two-tailed)	0.027	0.349	0.909	0.225
PTA 8000				
Pearson's correlation	−0.447*	−0.221	0.123	0.454
Significance (two-tailed)	0.013	0.241	0.518	0.112
BAEP-I				
Pearson's correlation	−0.011	−0.263	0.025	0.176
Significance (two-tailed)	0.955	0.160	0.897	0.351
BAEP-III				
Pearson's correlation	−0.539**	−0.140	0.151	−0.040
Significance (two-tailed)	0.002	0.459	0.426	0.833
BAEP-V				
Pearson's correlation	−0.510**	−0.020	0.104	−0.032
Significance (two-tailed)	0.004	0.916	0.585	0.867
BAEP-I–III				
Pearson's correlation	−0.462*	0.022	0.118	−0.132
Significance (two-tailed)	0.010	0.907	0.536	0.488
BAEP-I–V				
Pearson's correlation	−0.439*	0.117	0.078	−0.118
Significance (two-tailed)	0.015	0.538	0.682	0.535
BAEP-III–V				
Pearson's correlation	−0.014	0.167	−0.055	0.008
Significance (two-tailed)	0.941	0.378	0.773	0.967
cVEMP_P13				
Pearson's correlation	−0.358	−0.561	0.315	0.396
Significance (two-tailed)	0.132	0.112	0.189	0.093
cVEMP_N23				
Pearson's correlation	−0.468*	−0.211	0.454	0.214
Significance (two-tailed)	0.043	0.386	0.051	0.378
cVEMP P13_N23 amplitude				
Pearson's correlation	−0.038	0.033	0.185	−0.134
Significance (two-tailed)	0.878	0.894	0.449	0.586

BAEP, brainstem auditory-evoked potentials; cVEMP, cervical vestibular-evoked myogenic potential; PTA, pure tone average; VIDA, vitiligo disease activity score; *Correspondence to Correlation is significant at the 0.05 level (two-tailed); **Correlation is significant at the 0.01 level (two-tailed).

Similarly, Aydogan *et al.* [4] reported a statistically significant delay in the right ear of wave III and wave V latencies and in interpeak I–III latency. Moreover, a statistically significant delay in the left ear of wave III latency and in interpeak I–III was detected in patients with vitiligo compared with the control group. In contrast to our results, Shalaby *et al.* [9] and Mohamed *et al.* [26] found no statistically significant difference between vitiligo group and control group regarding BAEP findings.

Aydogan *et al.* [4] proposed that the delay of wave III, wave V, and interpeaks of I–V, I–III, and III–V of BAEP in patients with vitiligo may refer to the pathology of the superior olivary nucleus and upper brainstem or inferior colliculus and to abnormal synaptic activity and a delayed synchronization of the action potential along the pathway from the auditory nerve to the cochlear nucleus and from the cochlear nucleus to the superior olivary nucleus and inferior colliculus [28].

Regarding cVEMP results, cVEMP was absent bilaterally in eight (26.6%) of 30 and absent unilaterally in six (20%) of 30 in the left ear. Regarding the remaining 53.3% of patients with vitiligo, six of them showed normal cVEMP response and 10 (33.3%) patients showed bilaterally preserved cVEMP response.

P13 and N23 mean latencies were statistically significantly longer in patients with vitiligo compared with controls. There was no statistically significant difference regarding mean P13–N23 amplitudes between controls and patients with vitiligo. IAAD ratio was abnormal (prolonged) in 1/10 of patients with vitiligo (10%) and normal in 9/10 (90%) of patients. In 46.6%, IAAD could not be calculated (Table 3).

Mahdi *et al.* [25] found a statistically significant increase in P13 latency of cVEMP in the left ears of patients of vitiligo compared with the control group. They also reported no statistically significant difference between both the groups regarding N23 latency and P13–N23 amplitude of cVEMP.

Wright *et al.* [29] found in their animal study that the posterior superior portion of the membranous wall of the saccule is lined by melanocytes, and these cells play an effective role in regulating endolymph composition, which is responsible for modulation of the vestibular stimuli.

To the best of our knowledge, there is no study in the literature investigating VNG testing in patients with vitiligo. In this study, VNG results revealed that nine (30%) patients with vitiligo had canal paresis: three (10%) of them had right canal paresis, six (20%) left canal paresis, and one (3%) bilateral canal paresis. Moreover, nine (30%) patients showed spontaneous nystagmus, one (3%) patient had abnormal saccadic testing, and one (3%) had abnormal smooth pursuit. In addition, eight (26.6%) patients of nine patients with vestibular affection showed peripheral vestibular manifestations and one (3%) showed central vestibular manifestations (Table 4).

Melanocytes have been found in the endolymphatic sac, osseous spiral lamina, modiolus, stria vascularis, Reissner's membrane, ampullae, saccule, crus commune, and utricule [7,30]. Finding of previous studies revealed that the melanocytes of the cochlea and vestibular organ in the inner ear have useful roles in both hearing and balance [31].

Skin pigmentation is considered a sign of melanocyte function, so it is reasonable that vitiligo may be associated with destruction of the epithelium and disturbances of the inner ear (which contains melanocytes) [32].

In the present study, we found that there was no statistically significant correlation between age, disease activity, and extent of vitiligo and PTA, BAEP and cVEMP findings (Table 5). These results were in agreement with previous studies [25,26].

Surprisingly, we also found a negative statistically significant correlation between disease duration and PTA at 4 and 8 kHz; BAEP latencies of waves III and V and interpeaks of I–III and I–V, and latency of N23 of cVEMP (Table 5). This is in agreement with Elsaied *et al.* [14]. These results may indicate that the loss of the otic melanocyte function, if it happens it occurs mostly early in the disease then stabilized afterward [25].

Conclusion

This study revealed that melanin may have an important role in the maintenance of the function of the auditory and vestibular system. The presence of high-frequency hearing loss, BAEP abnormalities, and cVEMP are valuable findings in patients with vitiligo. This highlights the importance of follow-up

along the disease course for early detection of auditory abnormality. cVEMP testing can be used for the evaluation of the vestibulocolic reflex in patients with vitiligo. Moreover, VNG testing can be an important tool for assessment of the vestibular system in patients with vitiligo.

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Conflicts of interest

There are no conflicts of interest.

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