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Original article

Auditory and Vestibular Findings in Patients with Vitiligo: A Case – Control Study

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Abstract:
Background: Melanocytes disappearing from the skin as a result of a mechanism that is still unknown is the defining feature of vitiligo. Because vitiligo targets melanocytes throughout the body, not only those in the skin, the existence of melanocytes in the auditory and vestibular systems raises the possibility that these systems to be affected. There are some discrepancies in the research regarding how vitiligo affects hearing and vestibular systems. Accordingly, this study was conducted to evaluate audiological and vestibular involvement in vitiligo patients. **Subjects and methods:** A case-control study with 19 vitiligo patients and 19 healthy controls was conducted. Basic audiological and vestibular examination were performed on all patients and healthy controls including videonystagmography (VNG), cervical vestibular-evoked myogenic potential (cVEMP), and ocular vestibular-evoked myogenic potential (oVEMP). **Results:** There was a statistically significant difference were found in pure tone audiogram thresholds at 2,4, 8 KHz frequencies, caloric test, cVEMP and oVEMP parameters, between the vitiligo and the control groups. **Conclusion:** The study concluded that 78.9% of individuals with vitiligo experienced peripheral and/or central vestibular abnormalities, along with/without auditory impairment.

Keywords: Vestibular, auditory, vitiligo

INTRODUCTION:

Melanocytes, the skin's pigment-producing cells, are specifically targeted for destruction in vitiligo (the autoimmune skin disorder) by autoreactive clusters of differentiation T cells. Patients developed patchy white spots on their skin as a result. Approximately 1% of people have vitiligo**[1].** There are numerous hypothesized causes of vitiligo, including stress, autoimmune, genetic, neurological, melatonin receptor malfunction, decreased melanocyte migration, and/or proliferation, in addition to the accumulation of toxic intermediate products of melanin synthesis **[2].**

The elimination of the melanocytes is the disorder's final result, regardless of its source. In addition to the skin, melanocyte-containing organs such as the uveal tract, the retinal pigment epithelium, the leptomeninges, and the inner ear are also susceptible to this damage**[3].** Many melanocytes are present specifically in the modiolus, osseous spiral lamina, Reissner's membrane, and vascular stria of the human cochlea. Melanocytes are more common in highly vascularized regions with significant metabolic or secretory activity. Melanocytes are crucial for controlling the function of the skin of Na+/K+-ATPase and potassium channels to maintain the

electrical potential of the endocochlea and the functionality of hair cells**[4].**

The same pathophysiology between vitiligo and sensorineural hearing loss (SNHL) may be the cause of the connection between the two conditions. The potential causes of vitiligo that leads to SNHL include genetic variables, immunological responses, protein adhesion defects, and oxidative stress**[5].**

Melanocytes are present throughout the peripheral auditory system, but the involvement of brainstem, central auditory system, and vestibular system were also reported. Melanocytes can be found in the vestibular labyrinth: utricle, saccule, pars commune, ampulla, endolymphatic duct, and sac. The vestibular dysfunction could be explained by similar pathogenesis that explains the presence of SNHL**[4].**

There are many tests used in the assessment of vestibular system function; their results allow for accurate diagnosis of the cause. Videonystagmography (VNG) plays a major role in the diagnosis of dizziness and helps to differentiate the location of damage between the central and peripheral parts of the vestibular system**[6].**

Moreover, cervical vestibular-evoked myogenic potentials (cVEMP) and ocular vestibular-evoked myogenic potentials (oVEMP) are vestibular tests that are used to evaluate the otolith organs, these tests are capable of determining the participation of the superior and inferior nerves and, consequently, the utricular and saccular functions. Therefore, it may be beneficial to also look for latent and indirect vestibular system abnormalities in asymptomatic patients**[7].** This study aimed to detect the auditory and vestibular involvement in patients with vitiligo.

Subjects and methods:

Thirty- eight subjects were involved in a case - control study that was performed at the Audio-Vestibular Medicine unit, E.N.T Department, Faculty of Medicine, Zagazig University Hospitals during the period from April to October 2022. They were divided into two main groups; **Control group:** nineteen healthy subjects in the age range from 18 to 45 years old, without any prior history of vestibular or auditory problems, and **Study group:** nineteen patients have a definitive diagnosis of vitiligo. They matched the control in age and gender. Dermatologists with clinical experience made the vitiligo diagnosis. The types of disease are classified as, generalized (disseminated macules), localized (one or more macules in one area), acrofacial (involvement of the face and distal sections of the extremities), and acral vitiligo (involvement of extremities). The clinical features of all patients, including the duration and rule-of-nines-calculated percentage of body surface area (BSA) are affected by the disease**[8].** The exclusion criteria included family history of hearing loss, Chronic noise exposure, oral ototoxic medication use, head trauma, neurological, vascular, autoimmune, and other systemic diseases (e.g. diabetes or hypertension).

The Research Ethics Committee at the Faculty of Medicine, Zagazig University Hospitals approved this study. Written informed consent was obtained from all participants after the test procedures had been explained. The study was done according to The Code (IRB Number; 9458-3-4-2022) of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

METHODS:

All participants in the study were submitted to the following: full history taking; otological examination to ensure normal tympanic membrane and external auditory canal; basic audiological testing, such as Pure Tone Audiometry (PTA) by using Single-channel diagnostic audiometer, amplivox, for air conduction thresholds that were tested at frequencies from 0.25-8 kHz, whereas the examination of bone conduction thresholds was from 0.5-4 kHz; speech audiometry; and immittancemetry including tympanometry and acoustic reflexes were also done.

Vestibular system evaluation:

Videonystagmography (VNG): the following were done using VNG Ulmar version 0.1. These tests include Spontaneous nystagmus, Oculomotor tests (smooth pursuit, saccade, Optokinetic test), gaze fixation test, Positioning tests (Dix-Hallpike maneuver), Positional tests, and caloric test.

Cervical vestibular-evoked myogenic potential (cVEMP): was performed using otometrics Ics chartr EP200. EEG activity was measured. According to **Chou et al. [9]** three electrodes were used for recording of cVEMPs. Active electrode was placed on the sternocleidomastoid muscle of the neck's constricted middle third (SCM) on ipsilateral side. Reference electrode was on the upper sternum. Over forehead, a ground electrode was positioned.

The stimulation was done through headphones, tone burst at frequency of 500 Hz, and repetition rate: 5/sec. Intensity used was 95 dBnHL, and a bandpass filter was applied from 30-1500Hz. cVEMP response was judged as either present or absent according to

the presence or absence of P13–N23 biphasic response**[10].**

Ocular vestibular-evoked myogenic potential (oVEMP): three electrodes was used, active electrode was placed below the lower eyelid's midpoint. The reference electrode was positioned 1-2 cm underneath the active one. On the forehead, a ground electrode was positioned **[11].** The individual was told to lie on his back and keep looking up at a set mark in the ceiling **[12].** The stimulus parameters: Utilizing similar stimulus parameters of cVEMP, but the stimulus was delivered to the tested ear and recorded from contralateral eye.

Statistical Analysis:

The collected data were coded, entered, presented, and analyzed using the statistical package for social science (SPSS) version 26 database software program. Frequencies and percentages were used to represent qualitative data, and the Chi-square (X^2) test was used to determine whether different qualitative variables were related to one another. Quantitative variables were calculated using the mean, standard deviation (SD), and median with interquartile range (for data that were not normally distributed). The Mann-Whitney test was used to evaluate nonparametric data, while the independent sample t-test was used to determine differences when comparing normally distributed different quantitative variables. The results were categorized as statistically significant and extremely statistically significant when the significant probability (P value) was less than 0.05 and greater than 0.001, respectively.

RESULTS:

Two groups of adults were included in this study. The study group involved 19 patients (7 male and 12 female). The control group included 19 subjects (8 male and 11 female). There was no statistically significant difference between the vitiligo and control groups as regard age and sex, with no sex predilection in vitiligo group (Figure 1). Regarding pure tone audiometery, there was statistically significant difference between the vitiligo and control groups as regard 2000, 4000 and 8000 Hz in both ears (Table 1).

Regarding VNG, there was no statistically significant difference between the vitiligo and control groups in both spontaneous nystagmus and oculomotor abnormalities (saccade, smooth pursuit, optokinetic (OPK). Additionally, gaze nystagmus, positional, and positioning (Dix-Hallpik) tests showed no abnormalities (Table 2). Caloric weakness showed statistically significant difference between the vitiligo and control groups, and there was no statistical difference between them as regard directional preponderance (DP%) (Table 3). Moreover, the caloric weakness was reported in nine patients (47.4%), three of them (15.8%) showed bilateral weakness, and six others (31.6%) had unilateral weakness (Table 4).

VEMPs results in the vitiligo group showed that, there were two ases (10.5%) had absent cVEMP, three patients (15.8%) had reduced amplitude, and five patients (26.3%) had delayed latencies. Furthermore, delayed latencies were the most frequent abnormalities. In addition, there was statistically significant difference between the vitiligo and control groups as regard P1 latency, N1 latency, and P1-N1 amplitude in both ears. Also, there was a statistically significant difference between them as regards ratio % (Table 5). In the vitiligo group, there were two cases (10.5%) had absent oVEMP, four patients (21%) had reduced amplitude, and five patients (26.3%) had delayed latencies. Furthermore, delayed latencies were the most frequent abnormalities. There was a statistically significant difference between the vitiligo and control groups as regards P1 latency, N1 latency and, P1-N1 amplitude in both ears. Also, there was a statistically significant difference between them as regards ratio % (Table 6). There were 15 (78.9%) cases among the vitiligo group who suffered from vestibular disorders and/or auditory affection.

There was no significant correlation between vitiligo characteristics (duration and body surface area affected) and each of, PTA, SRT, WD, acoustic reflexes, saccade, Smooth pursuit, OPK, and caloric tests. Moreover, there was no significant correlation between the duration and body surface area affected and the VEMPs.

Table (1): Comparison of PTA between the vitiligo and control groups.

Variable		Vitiligo Group (n=19)	Control Group (n=19)	Tests	
				t	*P*
250 Hz Mean±SD Range	**Right**	12.37±3.06 (10 – 20)	10.79±1.87 (10 – 15)	1.919	0.063
	Left	13.42±5.28 (10 – 20)	11.84±2.48 (10 – 15)	1.179	0.246
500 Hz Mean±SD Range	**Right**	12.37±3.06 (10 – 20)	12.63±2.56 (10 – 15)	0.287	0.775
	Left	13.95±4.27 (10 – 20)	12.63±2.56 (10 – 15)	1.150	0.258
1000 Hz Mean±SD Range	**Right**	13.16±3.42 (10 – 20)	12.37±2.56 (10 – 15)	0.805	0.426
	Left	13.16±3.80 (10 -25)	12.89±2.54 (10 – 15)	0.251	0.803
2000 Hz Mean±SD Range	**Right**	14.47±2.84 (10 – 30)	12.37±2.56 (10 – 15)	2.400	**0.022***
	Left	15.79±4.49 (10 – 30)	12.63±2.56 (10 – 15)	2.661	**0.012***
4000 Hz Mean±SD Range	**Right**	16.32±7.23 (10 – 35)	12.89±2.53 (10 – 15)	1.94	**0.04***
	Left	19.47±6.85 (10 – 35)	13.16±2.48 (10 – 15)	0.006	**0.001***
8000 Hz Mean±SD Range	**Right**	22.63±7.88 (10 – 40)	13.42±3.36 (10 -20)	0.005	**<0.001***
	Left	22.37±9.18 (10 – 40)	13.42±3.36 (10 – 20)	0.002	**<0.001***

Table (2): Comparing vitiligo and control groups regarding VNG abnormalities.

Item	Category	Vitiligo		Control		X^2	P value
		N	%	N	%		
Spontaneous nystagmus	**Yes**	2	10.50	0	0	2.11	0.146
	No	17	89.5	19	100		
occulomotor	**Abnormal**	3	15.8	0	0	3.25	0.07

Table (3): Comparison of caloric test between the vitiligo and control groups

Variable	Vitiligo Group (n=16)	Control Group(n=19)	Tests	
			Za	*P*
weakness % Mean±SD Median (IQR)	21.06±20.94 14(1-66)	6.26±4.46 6 (2-14)	**2.633**	**0.009****
DP % Mean±SD Median (IQR)	9.75±9.17 7 (4.25-13.5)	5.74±4.05 5 (2-9)	**1.505**	0.131

[a]**Mann Whitney test**

Table (4): Number and percentage of the patients with caloric weakness and directional Preponderance in the vitiligo group

Variable	n. of cases (%) n= 19
Caloric weakness: 9 (47.4%)	
Bilateral	3 (15.8%)
Unilateral Right Left	6(31.6%) 2(10.5%) 4 (21%)
DP: 2 (10.5%)	
Right	1(5.3 %)
Left	1 (5.3%)

Table (5): Comparison of cVEMP between the vitiligo and control groups.

Variable		Vitiligo Group (n=19)	Control Group (n=19)	Tests	
				t	*P*
Right Mean±SD	**P1 latency**	15.31±2.22	13.83±0.87	2.690	**0.011***
	N1 latency	25.42±2.31	23.91±0.82	2.685	**0.011***
	P1-N1 amplitude	34.02±11.93	48.30±10.08	3.890	**<0.001***
left Mean±SD	**P1 latency**	16.03±2.36	13.97±0.71	3.626	**0.001***

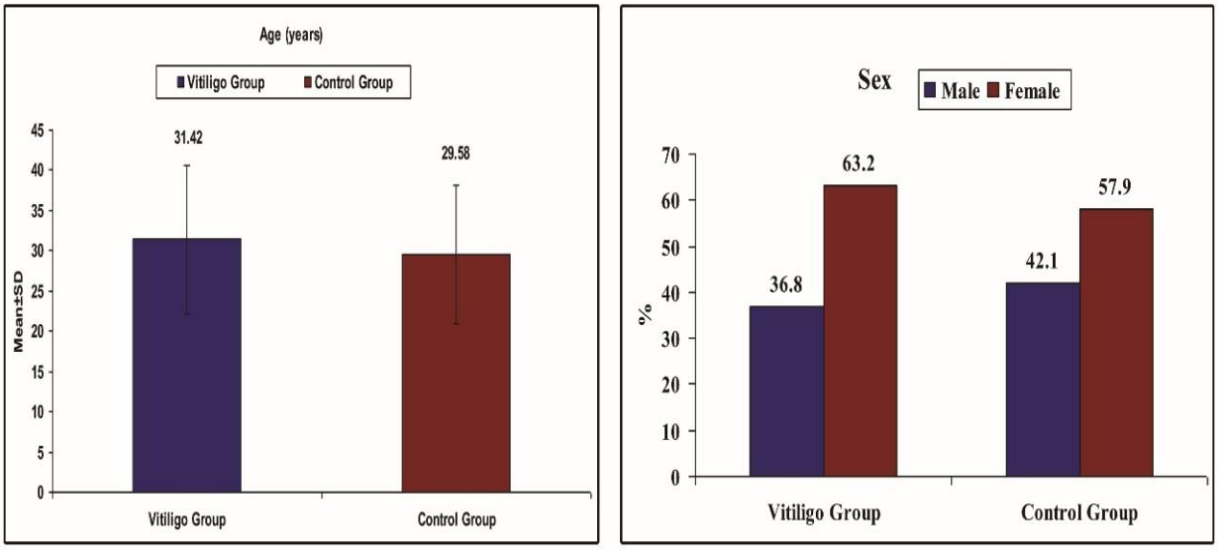

Figure (1): Age and gender distribution the vitiligo versus control group

DISCUSSION:

Vitiligo is an acquired pigmentary disorder of unknown etiology, clinically characterized by whitish macules caused by selective loss of melanocytes. About 50% of cases of vitiligo are documented before the age of 20, however, the disease's later onset may be linked to conditions like rheumatoid arthritis and diabetes mellitus (DM) **[13].**

As a systemic disease, vitiligo can affect the melanocytes in tissues other than the skin, such as the eyes and ears. Melanocytes can be found in the vestibular organs as well as the stria vascularis and modiolus of the cochlea**.** Due to the relationship between auditory melanocyte function and the hearing process, hearing loss could result from their destruction **[14].**

Two groups were included in this study and showed that, regarding age and sex, there is no statistically significant difference between the vitiligo and control groups, with no sex predilection in vitiligo group (Figure 1).

In the current study, pure tone thresholds were significantly higher in vitiligo group, mainly at 2000, 4000 and 8000 Hz frequencies in both ears (Table 1). This demonstrated the presence of significant high frequency SNHL in these patients "mild degree".

In agreement with the present study, **Mahdi et al. [7]** showed that when compared to control subjects, vitiligo patients' audiometry thresholds at 2, 4, and 8 kHz were statistically higher in both ears. Similarly, **Lien et al. [15]** showed that the pure tone audiometery of the vitiligo group and the control groups significantly differed at 2000, 4000, and 8000 Hz. Also, **Abd El Mageed et al. [16]** and **Dawoud et al. [17],** found that PTA showed significant difference in scores that were found between the study and control groups at the same frequency.

A key component of cryoprotection is melanin. Melanin reduces ototoxic environment-induced free radical damage by the Ca^{2+} chelator influences calcium homeostasis in cationic exchange, which in turn controls redox balance and shields cells from DNA damage. Additionally, melanocytes control potassium channels that are critical for the transmission of auditory function signals and are associated with the endocochlear electrical potential. The cochlear base, which is solely responsible for high-frequency hearing, contains the highest concentrations of melanin. When anti-melanocyte antibodies in vitiligo attack the melanocytes in the inner ear, less melanin is produced, which makes people more susceptible to high-frequency SNHL**[15]**. The maintenance of the endolymph, perilymph, and ionic equilibrium as well as the facilitation of substance exchanges by melanin suggest that it may play a significant role in cellular metabolism**[13].**

In disagreement with the current study, **Rahimi et al. [3]** demonstrated that they discovered no discernible difference between the case and control groups in any of the investigated frequencies when comparing the means of pure tone thresholds. The dissimilarity in the results of different studies may be explained as a consequence of the different ethnicities of the populations examined**[18].**

As regards the VNG test, we reported that there was two (10.5%) patients had spontaneous nystagmus and three (15.8%) cases had oculomotor abnormalities (saccade, smooth pursuit, and OPK) in vitiligo group. As regards gaze nystagmus, positional, and positioning (Dix-Hallpik), there were no reported abnormalities in these tests (Table 2). In agreement with the present study, **Koura et al. [19]** reported that 30% of patients showed spontaneous nystagmus, 3% had abnormal saccadic testing results, and 3% had abnormal smooth pursuit.

Additionally, **Abd El Mageed et al. [17]** showed that, 12% of patients had spontaneous nystagmus, 6.3% of patients had abnormal smooth pursuit and saccadic testing results. As regards gaze nystagmus and positional tests, they revealed no abnormal findings. However, they reported a positive Dix–Hallpike maneuver in two cases (3.2%). The exact site of damage in vitiligo is not known. **Aydogan et al. [20]** noticed that vitiligo patients have abnormalities in the cranial nerve VIII, above the level of the cochlear nuclei in the pons, and in the upper portion of the auditory pathway. This may be explained the central vestibular abnormalities.

In caloric test, the vitiligo and control groups differed statistically significantly as regards caloric weakness and there was no statistically difference between them as regard DP% (Table 3). This denotes the presence of peripheral compensated vestibular lesion. In agreement with present study, **Dawoud et al. [17]** showed that the vitiligo and control groups differed statistically significantly as regards caloric weakness. Similarly, **Abd El Mageed et al. [17]** reported similar results.

In the current study, the caloric weakness showed the highest percentage in nine cases (47.4%), the unilateral pathological response was in six patients (31.5%), (15.8% were right and 10.5% were left), while three patients (15.8%) had a bilateral pathological response (Table 4).

In agreement with the current study, **Koura et al. [19]** showed that (30%)of patients had canal weakness : 10 percent showed right canal weakness, 20% had left canal weakness, and 3% had bilateral canal weakness. In addition, **Abd El Mageed et al. [17]** revealed that, caloric test showed that 19% of patients with vitiligo had canal weakness 6.3% had right canal paresis and 9.5% had left canal weakness, and 3.2% had bilateral canal weakness. Also, **Manno et al.[11]** showed that unilateral pathological response present in 14% of patients, and 9% had a bilateral pathological response. Although the specific cause of the vestibular affection in vitiligo is uncertain, the following facts support the idea that

melanocytes may be responsible: (a) they arise from the neural crest, (b) they are situated in the vestibular labyrinth and the cochlea, (c) they are found in the leptomeninges that cover the vestibular ganglion and vestibular nerve, (d) they are attached to the wall of blood vessels**[17].**

cVEMP and oVEMP results showed the vitiligo and control groups differed significantly as regards P1 latency, N1 latency and P1-N1 amplitude in both ears. Also, there was statistically significant difference between them as regards ratio %. Additionally, delayed latencies were the most frequent abnormalities in both VEMPs (Tables 5, 6).

In agreement with our study, **Abd El Mageed et al. [17]** showed that latency of P1 and N1 waves showed a significant difference between controls and patients while the amplitude measured in both ears and amplitude ratio showed no difference between the two groups. Additionally, **Manno et al. [11]** reported that the vitiligo cases and controls differed statistically significant as regards VEMP abnormalities. This may be explained by the fact that the vestibular system's melanocytes are more abundant in the ampulla and dark cell region of the utricle than in the saccule and other semicircular canals. The marginal and intermediate cells of the stria vascularis serve a similar purpose to subepithelial melanocytes and the dark cell epithelium. They may therefore be helpful for maintaining endolymph balance **[11].**

CONCLUSION:

Regardless of the duration or location of the disease, some vitiligo patients suffer auditory and vestibular defects. Vitiligo sufferers had peripheral compensated vestibular lesion. According to the study's findings, peripheral and central vestibular abnormalities, either with or without auditory impairment, affected 78.9% of vitiligo patients. Every patient with vitiligo needs regular observation and audiological assessments for early identification and monitoring of changes as the disease progresses.

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