Auditory system dysfunction in patients with vitiligo: is it a part of a systemic autoimmune process?

Enass S. Mohamed[a], Eman A. Said[a], Doaa S. Sayed[b], Sara M. Awad[b], Marwa H. Ahmed[c]

Departments of [a]Otolaryngology, [b]Dermatology and Venereology, Faculty of Medicine, [c]Audiology Unit, Department of Otolaryngology, Assiut College of Medicine, Assiut University, Assiut, Egypt

Correspondence to Eman A.F. Said, MD, Audiology Unit, Department of Otolaryngology, Assiut College of Medicine, 71526 Assiut, Egypt; Tel: +01007238234; fax: +0882333327; e-mail: emanelgendy40@yahoo.com

Received 17 January 2017
Accepted 15 May 2017

The Egyptian Journal of Otolaryngology
2017, 33:594–602

Background and aim
Association of vitiligo with ocular and auditory abnormalities and other autoimmune disorders suggests its systemic autoimmune origin. Therefore, this study was carried out in an attempt to evaluate the effect of melanin deficiency in patients with vitiligo, as regards the extent and duration of the disease on the auditory pathway and to study the associated other ocular and systemic abnormalities in them.

Patients and methods
Forty patients with vitiligo and 20 normal volunteers were examined. Audiological evaluation including pure-tone audiometry, extended high-frequency audiometry, transient evoked otoacoustic emissions, and auditory brainstem response was carried out. Ophthalmic evaluation including visual acuity, intraocular tension, and fundus examination was carried out. Laboratory investigations including hemoglobin level, random blood sugar, liver, kidney, and thyroid function tests, and autoimmune testing (antistreptolysin O titer, erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibodies) were carried out.

Results
Sensorineural hearing loss was found in 15 (37.5%) patients; 10 (66.67%) of them had bilateral hearing loss and at high frequencies (2–8 kHz) sensorineural hearing loss. Transient evoked otoacoustic emissions were absent or decreased in 67.5%. There were no statistically significant differences in all auditory brainstem response parameters in vitiligo patients compared with the control group. One-fourth (25%) of them had decreased visual acuity, 22.5% had anemia, 12.5% had thyroid dysfunction, 10% had raised random blood sugar, 2.5% had raised liver enzymes, 32.5% had raised rheumatoid factor, 20% had raised antinuclear antibody, and 15% had raised erythrocyte sedimentation rate.

Keywords:
auditory, autoimmune, ocular dysfunction, systemic process, vitiligo

Egypt J Otolaryngol 33:594–602

1012-5574

Introduction

Vitiligo is an acquired depigmentary disorder that causes destruction of melanocytes in the skin, hair bulbs, mucous membranes, uveal tract and retinal pigment epithelium of the eyes, inner ear, and leptomeninges [1].

Although loss of melanocytes from the skin is almost always the primary and initial symptom in vitiligo, other pigment cells in the body can be affected [2].

Cochlear melanocytes may be affected in vitiligo and interfere with the conduction of action potentials in the auditory pathway. Melanocytes are not confined to the peripheral auditory system; they are also present in the central auditory system [3]. Damage can also occur to melanocytes within the iris and retina of the eyes [4].

The affection of extracutaneous melanocytes (auditory and ocular) in some patients with vitiligo and the presence of other autoimmune disorders in association with vitiligo suggest that systemic immunological events directed against pigment cells might play a role in the development of the disease. Therefore, vitiligo may be a part of systemic autoimmune process [5].

This study attempted to evaluate the effect of melanin deficiency in patients with vitiligo on the auditory pathway, to study the associated ocular and systemic abnormalities in vitiligo patients, and to study the effect of disease distribution and extent on these findings.

Patients and methods

Patients

The study group included 40 patients (27 female and 13 male). Their ages ranged from 18 to 40 years. All patients were free of middle ear disorders and had normal tympanograms.

The control group included 20 healthy volunteers matched with the study group for age and sex; they had normal peripheral hearing and normal middle ear function.

Exclusion criteria for both the study and the control group were a history of ototoxic drug intake, noise exposure or head trauma, tympanic membrane perforation, or middle ear disorder.

Informed consent was obtained from all participants in the study. The study was approved by the Ethics Committee of Assiut Medical University.

Methods

Dermatological evaluation (by a specialized dermatologist)

Dermatological evaluation by a specialized dermatologist included the following: detailed dermatological history from the patients, including family history of vitiligo, type, site, duration, onset and course of vitiligo, and history of other associated disorders such as diabetes mellitus, thyroid dysfunction, systemic lupus erythematosus, or rheumatoid arthritis. Full dermatological examination was carried out and patients were classified into four groups: generalized, focal, segmental, and acrofacial vitiligo [6]. Approximate percentage of the body surface area involved was calculated using the rule of nine according to the Vitiligo European Task Force system [7].

Audiological evaluation

All patients and controls were subjected to the following:

(1) Otological history taking.
(2) Otoscopic examination.
(3) Basic audiological evaluation in double-wall sound-treated booth (IAC model 1602A-t; Industrial Acoustic Company, USA) using dual-channel clinical audiometer (Madsen model Orbiter 922; GN Otometrics, Copenhagen, Denmark) and headphones TDH 39 [including pure-tone audiometry (PTA) air conduction (0.25–8 kHz) and bone conduction (0.5–4 kHz), speech audiometry; speech recognition threshold and speech discrimination score and immittancemetry using impedance audiometer, Interacoustics AZ 26; Denmark].
(4) Extended high-frequency audiometry at frequencies 10, 12, 16, 18, and 20 kHz using dual-channel clinical audiometer (Madsen model Orbiter 922; GN Otometrics and Sennheiser HDA-200 Headphone; Sennheiser).
(5) Transient evoked otoacoustic emissions (TEOAEs) using Intelligent Hearing System for TEOAEs (USA).
(6) The participant was instructed to remain as quiet as possible and the probe was properly fitted in the participant's outer ear canal using a foam ear tip so that the TEOAEs would be properly recorded. TEOAEs were performed using a wide-band click in continuous mode with an intensity of 80 dBSPL and a number of sweeps of 1024 pulses/s. Parameters considered in TEOAE testing were signal-to-noise (S/N) ratio of greater than or equal to 6 dB in at least three tested frequency bands [8].
(7) Auditory brainstem response (ABR) using evoked response audiometer (version 2; Nicolet Spirit, USA).

The electrodes were placed as follows: active electrode at the vertex (Cz), reference, and ground electrodes at the left and right ears (A1 and A2) and recording between vertex and ear (Cz-A1 for the left side and Cz-A2 for the right side).

Impedance was maintained below 5 kΩ. The following parameters were considered: the stimulus used was click with alternating polarity, intensity of 90 dBHL and duration of 0.1 ms, filter was 150–3000 Hz bandpass, time window was 10 ms, number of sweeps was 1500/s and rate of averaging was 21.1 Hz for low repetition rate (LRR) and 61.1 Hz for high repetition rate (HRR).

Responses were duplicated to ensure reproducibility. The peaks identified during ABR recording and determined for each ear separately were absolute latencies of waves I, III, and V, interpeak latencies of waves I–III, III–V, and I–V at LRR, absolute latency of wave V at HRR, difference between wave V latencies at LRR and HRR in each ear (intra-aural) and difference between the two ears with regard to wave V latencies at both LRR and HRR (interaural).

Ophthalmic evaluation (by a specialized ophthalmologist)

Opthalmic evaluation including a history of visual problems, visual acuity, intraocular tension, and fundus examination was carried out.

Laboratory investigations

Vitiligo patients underwent the following laboratory investigations: hemoglobin level, random blood sugar, liver and kidney function, thyroid function (T_3, T_4, and thyroid-stimulating hormone), autoimmune profile [antistreptolysin O titer (ASOT), erythrocyte sedimentation rate (ESR), rheumatoid factor, and antinuclear antibody (ANA)].

Statistical analysis

Data were collected and analysis was performed using the computer program IBM SPSS (SPSS Inc, Chicago, Illinois, USA), statistics (version 20). Data were expressed as mean±SD using Student's *t*-test to determine significance for quantitative variables and χ^2 to determine significance for qualitative variables. Furthermore, correlations between different parameters were assessed using Pearson's correlation test.

In all statistical procedures, *P*-value greater than 0.05 is considered nonsignificant, *P*-value less than 0.05 as significant, and *P*-value less than 0.01 as highly significant.

Results

The mean ages of vitiligo patients and healthy controls were 29.33±8.03 and 31.1±6.3 years, respectively. Sex distribution was as follows: 27 (67.5%) female and 13 (32.5%) male patients in the study group and 14 (70%) female and six (30%) male patients in the control group.

The mean duration of vitiligo was 9.84±7.24 years and the mean percentage of body surface area involved was 5.16±6.54%. Other associated systemic disorders and the laboratory data of patients are presented in Table 1 and 2.

Results of audiological evaluation

Fifteen (37.5%) patients had sensorineural hearing loss (SNHL) according to the results of conventional PTA (hearing threshold of >25 dB at any frequency according to ANSI 1969). Moreover, it showed that sex has no effect on the occurrence of hearing loss in vitiligo (Table 3).

Table 1 Characteristic features of vitiligo in the study group and other associated systemic disorders

	Study [*N* (%)]
Vitiligo onset	
Gradual	32 (80)
Sudden	8 (20)
Vitiligo course	
Progressive	34 (85)
Regressive	3 (7.5)
Stable	3 (7.5)
Type of vitiligo	
Generalized	22 (55)
Localized	18 (45)
Family history of vitiligo	
Yes	14 (35)
No	26 (65)
Associated autoimmune disease	
Yes (SLE and RA)	3 (7.5)
No	37 (92.5)
Associated systemic disease	
Yes (thyroid disorder and hepatitis)	4 (10)
No	36 (90)
Associated auditory C/O	
Yes (hearing loss, tinnitus, and vertigo)	12 (30)
No	28 (70)
Associated visual C/O	
Yes	0 (0)
No	40 (100)

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Table 2 The laboratory data for the study group

	Normal range	Study [*N* (%)]	
		Normal	Abnormal
Hemoglobin level	12–16 g/dl	31 (77.5)	9 (22.5)
Liver function tests	ALT≤40 IU/l AST≤40 IU/l Total bilirubin≤17 μmol/l	39 (97.5)	1 (2.5)
Kidney function tests	Urea≤40 mg/dl Creatinine≤1.4 mg/dl	40 (100)	0 (0)
Random blood sugar	≤200 mg/dl	36 (90)	4 (10)
Thyroid function tests	T_3≤0.8–2.1 ng/ml T_4≤4.6–12.5 μg/dl TSH≤0.5–5 μIU/ml	35 (87.5)	5 (12.5)
Autoimmune profile			
ASOT	≤200 IU/ml	35.5 (87.5)	5 (12.5)
ESR	First hour=0–7 mm Second hour=10–17 mm	34 (85)	6 (15)
RF	≤8 IU/ml	27 (67.5)	13 (32.5)
ANA	<1A.I.	32 (80)	8 (20)

A.I., activity index; ALT, alanine transaminase; ANA, antinuclear antibody; ASOT, antistreptolysin O titer; AST, aspartate transaminase; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; TSH, thyroid-stimulating hormone.

There was a statistically significant elevation in the mean values of hearing thresholds at frequencies 4, 8, and 10 kHz for the study group when compared with the corresponding values for the control group (at $P<0.05$) (Table 4).

The degree, side, and configuration of hearing loss in the study group are shown in Table 5. Most of them (11/15; 73.3%) had hearing loss of mild degree and 10/15 (66.7%) had bilateral high-frequency hearing loss.

Statistically significant differences were found in the mean values of S/N ratio of TEOAEs at all tested frequency bands and overall responses for the study group when compared with the corresponding values for the control group (at $P<0.05$) (Table 6).

No statistically significant differences were found in all tested ABR parameters for the study group when compared with the corresponding parameters for the control group (at $P>0.05$) (Table 7).

It was found that vitiligo patients with a longer disease duration (>5 years), more disease severity (>5% of body surface area involved), generalized type of vitiligo, and abnormal autoimmune profile had higher hearing thresholds at conventional and high-frequency audiometry and lower S/N ratio values and overall responses of TEOAEs but did not reach the level of statistical significance. This suggested that serial audiological follow-up is needed for those groups.

In addition, raised rheumatoid factor and/or ANA were found in the majority of patients with hearing loss, and hence serial audiological follow-up may be considered important for those patients compared with others with raised ASOT and ESR (Fig. 1).

Table 3 Number and percentage of participants with hearing loss in the study and control groups according to their sex distribution

Sex	Normal hearing	Hearing loss	*P*-value
Study [*N* (%)]			
Male (*n*=13)	6 (46.15)	7 (53.85)	0.095
Female (*n*=27)	19 (70.37)	8 (29.63)	
Control [*N* (%)]			
Male (*n*=6)	6 (100)	0 (0)	–
Female (*n*=14)	14 (100)	0 (0)	

Table 4 Results of pure-tone audiometry (conventional and extended high frequency) in both the study and control groups

Frequencies (kHz)	Study (*X*±SD)	Control (*X*±S.D)	*P*-value
Conventional PTA			
0.25	20.56±7.29	18.75±4.77	0.157
0.5	19.38±7.65	17.5±5.66	0.172
1	16.94±7.44	15.13±5.37	0.173
2	14.38±7.22	13.13±6.86	0.365
4	16.5±10.54	11±6.96	0.040*
8	18.81±9.88	13.13±7.13	0.002**
High-frequency PTA			
10	32.25±12.3	27.13±9.33	0.022*
12	35.44±16.31	33.63±9.34	0.516
16	64.13±19.42	60.75±22.55	0.397
18	78.63±15.81	78.38±10.88	0.929
20	85.81±12.21	82.63±11.32	0.170

PTA, pure-tone audiometry. **P*-value less than 0.05 as significant. ***P*-value less than 0.01 as highly significant.

Table 5 Degree, side, and configuration of hearing loss in the study group

	Study [*N* (%)]
Degree of HL	
Mild	11 (73.33)
Moderate	4 (26.67)
Side of HL	
Bilateral	10 (66.67)
Unilateral	5 (33.33)
Configuration of HL	
High frequencies (2–8 kHz)	10 (66.67)
Low frequencies (0.25–0.5 kHz)	3 (20.0)
All frequencies (0.25–8 kHz)	2 (13.33)

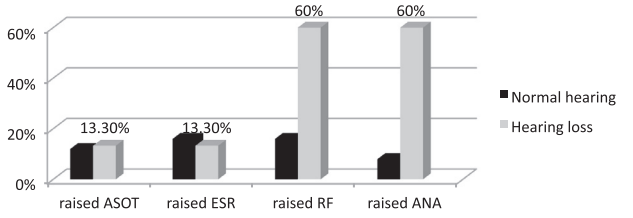
HL, hearing loss.

Table 6 Results of transient evoked otoacoustic emissions in both the study and control groups

TEOAEs S/N ratio (kHz)	Study (*X* ±SD)	Control (*X* ±SD)	*P*-value
1	8.53±6.02	19.67±6.17	0.001**
1.5	10.65±6.86	20.26±4.78	0.001**
2	10.1±6.46	19.66±5.36	0.001**
3	9.83±6.12	19.34±5.62	0.001**
4	4.05±4.43	10.87±5.65	0.001**
Overall response	15.57±3.46	22.08±3.32	0.001**

S/N, signal-to-noise; TEOAE, transient evoked otoacoustic emission. **Statistically significant differences between the study and control groups.

Figure 1



Histogram presented the percentage of patients with raised different autoimmune tests in both the normal hearing and hearing loss groups. ANA, antinuclear antibody; ASOT, antistreptolysin O titer; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Table 7 Results of different auditory brainstem response parameters at both low repetition rate (21.1/s) and high repetition rate (61.1/s) for both the study and the control group

ABR parameters	Study (*X*±SD)	Control (*X*±SD)	*P*-value
At LRR (21.1/s)			
Wave I	1.59±0.14	1.59±0.14	0.867
Wave III	3.71±0.25	3.7±0.23	0.801
Wave V	5.61±0.28	5.54±0.29	0.268
Interpeak I–III	2.12±0.25	2.12±0.23	0.874
Interpeak III–V	1.89±0.38	1.84±0.33	0.485
Interpeak I–V	4.01±0.33	3.96±0.31	0.368
Interaural latency	0.1±0.08	0.08±0.08	0.332
At HRR (61.1/s)			
Wave V HRR	5.87±0.26	5.8±0.28	0.191
Intra-aural wave V LRR and HRR	0.27±0.09	0.26±0.09	0.650
Interaural latency	0.08±0.09	0.08±0.09	0.752

ABR, auditory brainstem response; HRR, high repetition rate; LRR, low repetition rate.

Results of ophthalmic evaluation

One-fourth (25%) of the patients had decreased visual acuity and four (10%) patients had ocular abnormalities (iris or retinal hypopigmentary disorders); nevertheless, none of them complained of visual impairment.

Longer disease duration and more disease severity were observed in vitiligo patients with ocular abnormalities compared with those without ocular abnormalities (at $P<0.05$) (Table 8).

However, neither the type of vitiligo nor the autoimmune profile had a statistically significant effect on the presence or absence of ocular abnormalities.

Relation between results of different audiological tests and presence or absence of ocular abnormalities

Patients with ocular abnormalities had elevated hearing thresholds for conventional and extended high-frequency audiometry when compared with the corresponding values in those without ocular abnormalities. The mean values of S/N ratio of TEOAEs at all tested frequency bands and overall responses were lower in patients with ocular abnormalities when compared with the corresponding values in those without ocular abnormalities. However, this difference did not reach the level of statistical significance (at $P>0.05$) (Table 9).

These findings confirmed the association of ocular abnormalities with peripheral auditory abnormalities in vitiligo patients and indicated the importance of serial ocular follow-up in vitiligo patients, mainly in those with hearing loss.

Table 8 Distribution of ocular abnormalities in vitiligo patients according to disease duration and severity

	Ocular abnormalities		*P*-value
	Present	Absent	
Duration	10.46±7.37	4.25±0.87	0.001**
Severity	5.46±6.78	2.39±2.84	0.033*

**Statistically significant differences between the study and control groups.

Table 9 Comparison between results of pure-tone audiometry (conventional and extended high frequency) in vitiligo patients according to their ocular findings

Frequencies (kHz)	Ocular abnormalities		*P*-value
	Present	Absent	
Conventional PTA			
0.25	23.8±6.3	21.3±6.5	0.476
0.5	18.8±6.3	18.8±7.1	0.981
1	18.8±7.5	17.1±6.6	0.642
2	17.5±12.6	13.6±6.7	0.288
4	26.3±12.5	14.3±7.8	0.066
8	23.8±8.5	16.7±8.9	0.131
High-frequency PTA			
10	28.4±9.8	27.5±6.5	0.858
12	36.3±11.1	30.9±14	0.459
16	72.5±18.5	65.6±23.6	0.572
18	90±7.1	85.4±12.6	0.479
20	95±0	92.4±5.6	0.366

PTA, pure-tone audiometry.

Discussion

Although loss of melanocytes in vitiligo patients is mainly confined to the skin, alterations in extracutaneous sites have been reported [5]. Otic melanocytes are primarily situated in the stria vascularis, modiolus of the cochlea, and vestibular organs [9]. They are not confined to the peripheral auditory system as both humans and animals with pigment disorders are found to have abnormalities in the auditory brainstem [3].

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 damaging factors such as ototoxic

drugs, noise exposure, and age-related hearing loss [10]. Melanin is supposed to have a significant role in the establishment and/or maintenance of the structure and function of the auditory system and may modulate the transduction of auditory stimuli in the inner ear [11].

Deficiency in otic melanocytes is associated with low K^+ composition in the endolymph indicating that those cells may facilitate K^+ transport directly or indirectly. Low K^+ in the endolymph could affect the hair cell response to the sound-induced motion of the endolymph [12].

Mitf (microphthalmia-associated transcription factor), which is a protein encoded by *Mitf* gene in humans, is involved in the pathway regulation of many types of cells, including melanocytes, and controls the expression of various genes that are essential for normal melanin synthesis; therefore, mutations of *Mitf* result in diseases with deafness and pigmentation disorders such as vitiligo, melanoma, Waardenburg syndrome, and Tietz syndrome [13]. The precise role of Mitf remains questionable but it is thought that it has an ongoing postdevelopmental role in cochlear function [14].

Many patients in the current study had vitiligo of gradual onset (80%), progressive course (85%), generalized type (55%), and positive family history of vitiligo (35%), and these results are in agreement with several studies [15,16].

Associated autoimmune disorders were found in three (7.5%) patients; two of them had systemic lupus erythematosus and one had rheumatoid arthritis. Other systemic disorders that may be of an autoimmune origin were found in four (10%) patients: two with hypothyroidism, one with hyperthyroidism, and one with raised liver enzymes. This is in agreement with some studies [17], whereas other previous studies found autoimmune disorders in a relatively smaller proportion of vitiligo patients [18].

In the present study, 22.5% of patients had anemia. This is in agreement with most studies, which reported nearly similar results [19]. Further, it was found that only one (2.5%) patient had raised liver enzymes (alanine transaminase and aspartate transaminase) and none had abnormal kidney function tests (serum urea and creatinine). Some previous studies agreed with these results [20], whereas others found abnormal liver and kidney function tests in a larger percentage of vitiligo patients [21]. This may be attributed to a wider age range of these studies (5–75 years). Random blood sugar was found to be raised in only 10% of patients; this is consistent with the findings of Shankar *et al.* [19], but in disagreement with the findings of Gopal *et al.* [16], who found diabetes mellitus in a larger proportion of patients.

In the current study, five (12.5%) patients had various thyroid dysfunctions. Some research studies are in agreement with these results [16,19] but others are in disagreement [21,22]. As regards autoimmune profile in this study, it was found that 32.5% of patients had raised rheumatoid factor, 20% had raised ANA, 15% had raised ESR, and 12.5% had raised ASOT. These results are in agreement with previous studies [19–23], whereas Darmian *et al.* [24] found a higher incidence of patients with raised rheumatoid factor.

In the present study, statistically significant differences were found between the study and control groups in hearing thresholds at frequencies 4, 8 and 10 kHz. These results are in agreement with some studies [2,8,25]. Hearing loss in vitiligo is attributed to the destruction of inner ear melanocytes, which have important functions, including maintenance of the normal function of the stria vascularis and the cochlea, development of endocochlear potentials and maintenance of ion and fluid gradient between the endolymph and perilymph [26]. However, other studies reported that the elevated hearing thresholds in vitiligo patients did not reach the level of statistically significant difference compared with the control group [27–29].

SNHL was found in 15 (37.5%) patients. This is in agreement with some researchers [25,30], whereas others found a lower incidence of hearing loss among their patients [27,29,31,32].

Both sexes were equally affected by SNHL (eight female and seven male). This is in agreement with the finding of Shankar *et al.* [19] and Sharma *et al.* [32], whereas other researchers found a higher incidence of hearing loss in male patients [2] or in female patients [30].

Moreover, it was found that, out of the 15 patients with SNHL, 10 patients had bilateral and high-frequency hearing loss, which is in agreement with the findings of Mahdi *et al.* [25] and Sharma *et al.* [32].

Although hearing loss was found in 15 patients, only 4 (10%) of them were complaining of hearing loss and

most of them showed hearing affection at extended high-frequency audiometry, reflecting the importance of extended high-frequency audiometry in the early detection of minimal affection of hearing [28].

Evaluation of cochlear function using TEOAEs revealed that there were statistically significant differences between the study and control groups in S/N ratio at all tested frequency bands and the overall responses. These results are in agreement with Munjal *et al.* [8] and Angrisani *et al.* [27], who reported that recording of TEOAEs was a sensitive test for early detection of cochlear dysfunction before symptoms become manifest.

The current study revealed that there were no statistically significant differences between the study and control groups in all tested ABR parameters. These results were consistent with some studies [3,28] but in disagreement with other studies, which found significant differences in ABR parameters in vitiligo patients [8,25,31,33–35]. This was attributed to the differences in both methodology and participants' characteristics.

There were no significant correlations between the age of the patients and the results of PTA, TEOAEs, and ABR; this is in agreement with previous studies [25,27,31].

In the present study, neither the disease duration nor its severity had any statistically significant effect on the results of different audiological tests studied (PTA: both conventional and high frequency, TEOAEs, and ABR). This is in agreement with some research studies [25,32] and in disagreement with others [16,27,34]. This is attributed to the possibility that otic melanocytes are affected at the start of vitiligo and then stabilize afterwards [25].

Although hearing loss was present in 60% of patients with generalized vitiligo and in 60% of patients with abnormal autoimmune profile, neither the type of vitiligo nor the autoimmune profile had any statistically significant effect on the results of different audiological tests studied. This indicated that vitiligo patients with generalized type of vitiligo and/or those with abnormal autoimmune profile should be serially audiologically assessed for early hearing loss detection.

This is in agreement with the findings of Angrisani *et al.* [27], but in disagreement with other researchers who found that hearing loss was significantly higher in those with generalized vitiligo [8,16,25,32]. As regards autoimmune profile, according to the author's best knowledge, there were no published papers on the relation of hearing loss in vitiligo with the abnormal autoimmune test(s), and hence more research would be needed to cover this point in the future.

Concerning the different autoimmune tests, vitiligo patients who had abnormally raised values of rheumatoid factor and ANA were associated with a higher percentage of hearing loss (60%) and this percentage was statistically significant when compared with those who had hearing loss and normal values of these laboratory tests, indicating that those laboratory tests may have more sensitivity compared with others (ASOT and ESR), but this warrants further research on a larger number of patients.

In the present study, although none of the patients complained of visual impairment, 10 (25%) patients had decreased visual acuity and 4 (10%) patients had ocular abnormalities (iris or retinal hypopigmentary disorders). These results are consistent with the findings of Biswas *et al.* [36] and Park *et al.* [37], but in disagreement with the findings of Gopal *et al.* [16]. This may be an indicator of the importance of serial ophthalmic evaluation of vitiligo patients for early detection and management of any ocular abnormality [36].

Disease duration and severity were significantly higher in patients with ocular abnormalities when compared with those without ocular abnormalities; these results are in agreement with the findings of Gopal *et al.* [16] and Biswas *et al.* [36], but in disagreement with the findings of Cowan *et al.* [38]. This was supported by the fact that ocular abnormalities were common associations with increasing duration and severity of vitiligo and the ocular melanocytes were more commonly affected as well as epidermal melanocytes. [36,39].

However, neither the type of vitiligo nor the autoimmune profile had any statistically significant effect on the presence or absence of ocular abnormalities. These results are in agreement with those of Biswas *et al.* [36] and Cowan *et al.* [38], whereas Gopal *et al.* [16] found that ocular abnormalities were significantly higher in patients with generalized vitiligo. As regards autoimmune profile, according to the author's best knowledge, there were no published papers on the relation of the presence of ocular abnormalities in vitiligo with the abnormal autoimmune test(s), and hence further research would be needed to cover this point in the future.

In this study, although patients with ocular abnormalities had elevated pure-tone thresholds for conventional and

extended high-frequency audiometry and had lower S/N ratio of TEOAEs at all tested frequency bands and overall responses when compared with those without ocular abnormalities, these differences did not reach the level of statistical significance. However, there may be an association of the ocular abnormalities with the peripheral auditory abnormalities in vitiligo patients. Therefore, further studies on a larger number of patients would be needed.

Conclusion

The results of this study add more evidence to the auditory and visual involvement and the presence of systemic associations in patients suffering from vitiligo. Both extended high-frequency audiometry and TEOAEs had the advantages of detecting early minimal affection of hearing sensitivity and in early detection of minimal cochlear dysfunction, respectively. Moreover, it was clarified that vitiligo could be presented as a systemic disease resulting from melanocyte involvement in all parts of the body and the triggering event mostly was an autoimmune pathogenesis.

Recommendations

Vitiligo patients should be subjected to both audiological and ophthalmological evaluations with regular follow-up for audiological abnormalities using extended high-frequency audiometry and TEOAEs, especially those with longer disease duration, more disease severity, generalized type of vitiligo and/or abnormal autoimmune profile even if they do not exhibit hearing difficulties. For ocular abnormalities, thorough examination of visual acuity and ocular fundi is recommended. To be able to extrapolate the findings of the study on the entire population, further studies with larger sample including all types of vitiligo are recommended.

Application of more specific laboratory tests such as anti-heat shock protein 70 and anti-cochline antibodies is recommended to prove the presence of possible autoimmune inner ear disease in vitiligo patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Kemp EH, Waterman EA, Weetman AP. Autoimmune aspects of vitiligo. Autoimmunity 2001; 34:65–77.

2 Ardiç FN, Aktan S, Kara CO, Sanli B. High-frequency hearing and reflex latency in patients with pigment disorder. Am J Otolaryngol 1998; 19:365–369.

3 Ozuer MZ, Sahiner T, Aktan S, Sanli B, Bayramoğlu I. Auditory evoked potentials in vitiligo patients. Scand Audiol 1998; 27:255–258.

4 Sharma L, Dixit SN, Kant S. Eye lesion in vitiligo. Q J Surg Sci 1999; 35:49–53.

5 Nordlund JJ, Ortonne JP, King R, Nordlund J, Boissy R, Hearing V. Vitiligo vulgaris. The pigmentary system: physiology & pathophysiology. Oxford, UK: Oxford University Press 1998. pp. 513–40.

6 Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CCE. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res 2012; 25: E1–E13.

7 Taïeb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res 2007; 20:27–35.

8 Munjal S, Arya R, Kumar N, Kanwar AJ. Audiological and electrophysiological changes in patients with vitiligo. Indian J Otolaryngol 2015; 8:89–95.

9 Steel KP, Barkway C. Another role for melanocytes: their importance for normal stria vascularis development in the mammalian inner ear. Development 1989; 107:453–463.

10 Murillo Cuesta S, Contreras J, Zurita E, Cediel R, Cantero M, Varela Nieto I. Melanin precursors prevent premature age related and noise induced hearing loss in albino mice. Pigment Cell Melanoma Res 2010; 23:72–83.

11 Trune DR. Ion homeostasis in the ear: mechanisms, maladies, and management. Curr Opin Otolaryngol Head Neck Surg 2010; 18:413–419.

12 Ando M, Takeuchi S. Immunological identification of an inward rectifier K^+ channel in the intermediate cell (melanocyte) of the cochlear stria vascularis of gerbils and rats. Cell Tissue Res 1999; 298:179–183.

13 Sato-Jin K, Nishimura EK, Akasaka E, Huber W, Nakano H, Miller A, *et al.* Epistatic connections between microphthalmia-associated transcription factor and endothelin signaling in Waardenburg syndrome and other pigmentary disorders. FASEB J 2008; 22:1155–1168.

14 Planque N, Raposo G, Leconte L, Anezo O, Martin P, Saule S. Microphthalmia transcription factor induces both retinal pigmented epithelium and neural crest melanocytes from neuroretina cells. J Biol Chem 2004; 279:41911–41917.

15 AlMutairi N, Al-Sebeih KH. Late-onset vitiligo and audiological abnormalities: is there any association? Indian J Dermatol Venereol Leprol 2011; 77:571–576.

16 Gopal KV, Rama Rao GR, Kumar YH, Appa Rao MV, Vasudev P, Strikant. Vitiligo: a part of a systemic autoimmune process. Indian J Dermatol Venereol Leprol 2007; 73:162-165.

17 Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 2003; 16:208–214.

18 Poojary SA. Vitiligo and associated autoimmune disorders: a retrospective hospital-based study in Mumbai, India. Allergol Immunopathol (Madr) 2011; 39:356–361.

19 Shankar DS, Shashikala K, Madala R. Clinical patterns of vitiligo and its associated comorbidities. Indian J Dermatol 2012; 3:114–118.

20 Limdi JK, Hyde GM. Evaluation of abnormal liver function tests. Postgrad Med J 2003; 79:307–312.

21 Boisseau-Garsaud AM, Garsaud P, Calès-Quist D, Hélénon R, Quénéhervé C. Epidemiology of vitiligo in the French West Indies (Isle of Martinique). Int J Dermatol 2000; 39:18–20.

22 Gawkrodger DJ, Ormerod AD, Shaw L. Guideline for the diagnosis and management of vitiligo. Br J Dermatol 2008; 159:1051–1076.

23 Zetting G, Tanew A, Fischer G, Mayr W, Dudczak R, Weissel M. Autoimmune diseases in vitiligo: do anti-nuclear antibodies decrease thyroid volume? Clin Exp Immunol 2003; 131:347–354.

24 Darmian FV, Joubeh S, Doroudchi M, Abdollahi B, Ghaderi A. Detection of rheumatoid factors in sera and biopsy lesions of vitiligo patients. Iran Med J 2004; 1:48–54.

25 Mahdi P, Rouzbahani M, Amali A, Khiabanlu SR, Kamali M. Audiological manifestations in vitiligo patients. Iran J Otorhinolaryngol 2012; 24:35–40.

26 Barrenãs ML. Hair cell loss from acoustic trauma in chloroquine-treated red, black and albino guinea pigs. Audiology 1997; 36:187–201.

27 Angrisani RM, Azevedo MF, Pereira LD, Lopes C, Garcia MV. A study on otoacoustic emission and suppression effects in patients with vitiligo. Braz J Otorhinolaryngol 2009; 75:111–115.

28 Shalaby MES, El-Zarea GA, Nassar AI. Auditory function in vitiligo patients. Egypt Dermatol Online J 2006; 2:7.

29 Tosti A, Batdazzi F, Tosti G, Monti L. Audiologic abnormalities in cases of vitiligo. J Am Acad Dermatol 1987; 17:230–233.

30 Sharifian MR, Maleki M, Honarvar H. The correlation between vitiligo and hearing loss. Iran J Otorhinolaryngol 2006; 17:3–8.

31 Aydogan K, Turan OF, Onart S, Karadogan SK, Tunali S. Audiological abnormalities in patients with vitiligo. Clin Exp Dermatol 2006; 31:110–113.

32 Sharma L, Bhawan R, Jain RK. Hypoacusis in vitiligo. Indian J Dermatol Venereol Leprol 2004; 70:162–164.

33 Bassiouny A, Farid S, El Khousht M. Hearing abnormalities in vitiligo. Egypt J Otolaryngol 1998; 15.1:51–60.

34 Elsaied MA, Naga YAA, Abdo IM. Evaluation of brainstem evoked response in vitiligo patients. J Pan-Arab League Dermatol 2008; 19:91–97.

35 Nikiforidis GC, Tsambaos DG, Karamitsos DS, Koutsojannis CC. Abnormalities of the auditory brainstem response in vitiligo. Scand Audiol 1993; 22:97–100.

36 Biswas G, Barbhuiya JN, Biswas MC, Islam MN, Dutta S. Clinical pattern of ocular manifestations of vitiligo. J Indian Med Assoc 2003; 101:478–480.

37 Park S, Albert DM, Bolognia JL. Ocular manifestations of pigmentary disorders. Dermatol Clin 1992; 10:609–622.

38 Cowan CL Jr, Halder RM, Grimes PE, Chakrabarti SG, Kenney JA Jr. Ocular disturbances in vitiligo. J Am Acad Dermatol 1986; 15: 17–24.

39 Albert DM, Nordlund JJ, Lerner AB. Ocular abnormalities occurring with vitiligo. Ophthalmology 1979; 86:1145–1160.