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Evaluation of brainstem auditory evoked potentials and their relationship with levels of thyroid autoantibodies in patients with vitiligo

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Background/aim: Vitiligo is a common depigmenting disorder. The damage can also occur in similar ways to melanocytes within other organs. We evaluated the brainstem and auditory pathway functions by evaluating brainstem auditory evoked potentials (BAEPs) and whether there is any relationship between auditory functions and autoimmunity.

Materials and methods: Forty patients with vitiligo and 20 healthy volunteers were enrolled. Thyroid functions and autoantibodies were examined and BAEP tests were assessed by a neurologist.

Results: Antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TGA) antibody positivity was higher in the patient group ($P < 0.05$). A negative correlation was detected between anti-TPO and lead III, IV, and V latency and I–III interpeak latency (IPL) of the right ear together with lead IV latency and I–V IPL of the left ear in the patient group. When each BAEP parameter was compared between the two groups, more abnormalities were detected in the V latency and III–V IPL of the left ear together with IV and V latency of the right ear.

Conclusion: In this study the presence of a correlation between increased anti-TGA and anti-TPO levels and BAEP parameters may be related to an autoimmune-mediated mechanism. However, further studies are needed to be performed in a large patient series.

Key words: Brainstem auditory evoked potentials, thyroid autoimmunity, vitiligo

1. Introduction

Vitiligo is a relatively common disease occurring as a result of functional melanocyte loss (1). The embryonic origin of human melanocytes is derived from the neural crest and is located in the epidermis, hair bulbs of the skin, the uveal tract and the retinal pigment epithelium of the eye, the inner ear, and the leptomeninges (2). Although the loss or reduction of melanocytes in the inner ear may have a critical effect on hearing, patients with vitiligo usually do not have remarkable audiological abnormalities. There have been few studies on hearing loss in vitiligo patients in different populations (2–7).

Vitiligo is a chronic acquired pigmentation disorder that occurs as a result of loss of functional melanocytes from the epidermis and hair follicles, clinically characterized by depigmented patches (8). Melanocyte is a critical cell to maintain normal functioning of the stria vascularis and cochlea. It is essential for hair cells, as well (6,9). In animal trials, it has been shown that low melanin levels in the cochlea may increase the tendency to develop auditory fatigue, noise-induced hearing loss, and audiogenic seizures (3). Abnormal brainstem auditory evoked potentials (BAEPs) were recorded in patients with albinism. Therefore, changes in pigment cells or melanocyte destruction can cause hearing problems (10).

A BAEP is a short-latency auditory evoked potential recorded with surface electrodes. The potentials have series of positive and negative waves that are recorded within 10 ms following the stimulus. BAEPs are useful to assess the lower auditory system and may be helpful to detect subclinical abnormalities in the auditory system (11).

Vitiligo is an autoimmune-mediated disease. Thyroid disease is the most common autoimmune disease that is accompanied by vitiligo. Several studies have shown

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that the frequencies of autoimmune thyroid diseases or abnormal thyroid tests are significantly higher in patients with vitiligo than control groups (12–14).

There are limited studies assessing hearing abnormalities in vitiligo patients in the literature and their results are controversial. Most patients with vitiligo are asymptomatic for audiological abnormalities (2–4,6). To date, an association between hearing loss and autoimmunity has not been assessed yet. Thus, we aimed to evaluate and identify possible subclinical electrophysiological abnormalities of the auditory system with BAEP testing in patients with vitiligo as well as the relationship between BAEP results and autoimmune thyroid diseases.

2. Materials and methods

2.1. Patients and controls

Forty patients with generalized vitiligo and 20 healthy volunteers of similar age and sex were enrolled in our study. The diagnosis was made based on medical history, physical examination, and Wood lamp examination without the need of biopsy in all cases. The study received ethics committee approval and written informed consent was obtained from all participating individuals. BAEP examinations for both ears were performed in the patient group and in the control group.

Patients who had history or evidence of audiological diseases; familial hearing loss; chronic noise exposure; head trauma; metabolic, neurological, vascular, or autoimmune disease; any systemic diseases such as diabetes or hypertension; age >50 years; or use of oral autotoxic or corticosteroids were excluded from the study.

2.2. Laboratory tests

Blood samples were analyzed for thyroid function assays and detection of thyroid autoantibodies. Free T3, free T4, thyroid-stimulating hormone (TSH), thyroglobulin, antithyroglobulin (anti-TGA), and antithyroid peroxidase (anti TPO) antibody levels were measured by immunoassay of hormones. Laboratory tests were measured with the ARCHITECT i4000SR Immunoassay Analyzer (Abbott).

2.3. Measurement of BAEPs

BAEPs were measured by using the Nihon Kohden Neuropack 2 EMG/EP measuring system and two recording channels with filter band-pass between 100 and 3000 Hz. This were based on the American EEG Society guidelines (15). Recording electrodes were attached on the vertex (Cz), mastoids, and a frontal location midway between the nasion and vertex (ground). During testing, all subjects reclined in a dark and quiet room. Monaural rarefaction clicks (90 dB, 0.1 ms in duration) were used as auditory stimuli. White noise at 40 dB to the contralateral ear was used. The sounds were produced by activating earphones with pulses of 0.1 ms at a rate of 8–10/s and an intensity of 70 dB above sensation level for the click. Analysis time was 100 ms with a system band-pass of 100–200 Hz. I, III, and IV wave latencies; amplitudes; and I–III, III–IV, and I–V interpeak latencies (IPLs) were measured and compared between the groups for each ear.

2.4. Evaluation of BAEPs

The increase of latencies and IPLs and the increase or decrease in amplitudes was considered as an abnormal. Prolongation in I–III IPL indicates a conduction defect in the pathway from the proximal eighth nerve into the inferior pons, increase in III–IV IPL indicates a defect between the midbrain and pons, and increase in I–V IPL indicates a defect from the peripheral cochlea to inferior colliculus (16). The first peak latency is primarily associated with the basilar membrane and hair cells in the cochlea. I–III IPL is related with transmission of the action potentials from the cochlear nucleus to the superior colliculus (3).

2.5. Statistical analysis

For statistical analysis, SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used. Descriptive statistics such as mean, median, standard deviation, and minimum and maximum values were used for continuous variables while numbers and percentages were used for categorical variables. The Mann–Whitney U test was used to compare two groups with continuous variables. To determine the relationship between these variables the Spearman correlation coefficient was used. Categorical variables were compared between groups with a chi-square test. $P < 0.05$ was considered to be statistically significant.

3. Results

The vitiligo group consisted of 17 females and 23 males with a mean age of 25 ± 9.38 years (range: 18–51), while the control group consisted of 7 females and 13 males with a mean age of 30 ± 8.15 years (range: 18–45 years). There were no statistically significant differences among groups with respect to age and sex ($P > 0.05$). Mean duration of the disease was 36 ± 73.94 months.

When each BAEP parameter was compared between the groups, there were statistically significantly more abnormalities in the vitiligo group in left V, left III–V, right IV, and right V parameters than in the control group (Table 1). The comparisons of differences in abnormal latency shifts showed statistically significantly more abnormalities in the vitiligo group than the control group ($P = 0.04$, Table 2). There were no statistically significant differences in decrease in amplitudes or increase in latencies and IPLs between the groups ($P > 0.05$).

When all thyroid parameters were measured, anti-TPO and free T4 values were statistically significantly higher and thyroglobulin values were lower in the vitiligo group than the control group ($P = 0.038$, $P = 0.029$, and P

Table 1. Comparison of BAEP and laboratory characteristics of study and control groups. Data with normal and skewed distributions are shown as mean ± standard deviation (SD).

Right (R) I	Patients, mean ± SD group	Control group, mean ± SD	P-value
	1.59 ± 0.21	1.61 ± 0.24	0.718
R III	3.75 ± 0.26	3.8 ± 0.42	0.559
R V	5.66 ± 0.27	5.65 ± 0.35	0.879
R I–V	4.08 ± 0.38	3.85 ± 0.83	0.157
R I–III	2.19 ± 0.34	2.18 ± 0.38	0.947
R III–V	1.90 ± 0.27	1.84 ± 0.33	0.487
R II	2.66 ± 0.33	2.79 ± 0.45	0.240
R IV	4.86 ± 0.31	4.80 ± 0.51	0.573
Left (L) I	1.61 ± 0.21	1.60 ± 0.29	0.967
L III	3.79 ± 0.29	3.78 ± 0.44	0.913
L V	5.69 ± 0.39	5.69 ± 0.17	0.981
L I–V	4.09 ± 0.34	4.09 ± 0.27	0.892
L I–III	2.24 ± 0.28	2.18 ± 0.37	0.453
L III–V	1.89 ± 0.31	1.91 ±0 .49	0.841
L II	2.59 ± 0.31	2.63 ± 0.45	0.691
L IV	4.83 ± 0.20	5.05 ± 0.39	0.08
Anti-TGA	51.52 ± 17.2	2.66 ± 3.46	0.172
Anti-TPO	114.84 ± 28.2	7.37 ± 3.24	0.038
Thyroglobulin	10.68 ± 11.32	19.55 ± 13.17	0.004
TSH	1.63 ± 1.08	1.37 ±0.79	0.323
Free T3	3.37 ± 1.66	2.99 ± 0.58	0.230
Free T4	1.25 ±0.40	1.07 ± 0.15	0.029

Abbreviations: TSH, thyroid-stimulating hormone; anti-TGA, antithyroglobulin antibody; anti-TPO, antithyroid peroxidase antibody.
Normal values of BAEP parameters: I–III interpeak latencies ≥2.5 ms, III–V interpeak latencies ≥2.4 ms, I–V interpeak latencies ≥4.5 ms.

= 0.04, respectively). The rate of anti-TGA positivity was statistically significantly higher in the vitiligo group than the control group (P = 0.024). There were no statistically significant differences in the other parameters between the two groups (P = 0.769, Table 1).

We analyzed the degree of correlation between BAEP parameters and thyroid autoantibodies. A statistically significant negative correlation coefficient (R = –0.348) (34.8%) was obtained between anti-TPO and right III (P < 0.05). Moreover, there was a statistically significant negative correlation between anti-TPO and right V, right I–III, right IV, left I–V, and left IV parameters (R = –0.386, –0.375, –0.541, –0.332, and –0.443, respectively) (P < 0.05). A negative correlation was found between anti-TPO and other BAEP parameters, but it was not statistically significant (P > 0.05). A statistically significant negative correlation was found between anti-TGA and right I–III, right IV, and left III parameters (R = –0.336, –0.353, and –0.331, respectively) (P < 0.05). All the other BAEP parameters showed negative correlations with anti-TGA, except for two parameters, but none of them were statistically significant. A statistically significant negative correlation (31.6%) was found between the left III–V parameter and free T3 (P < 0.05). A significant correlation

Table 2. Comparison of abnormal cases of BAEP parameters in study and control groups.

	Patient group		Control group		P-value
	Normal	Abnormal	Normal	Abnormal	
R I	37	3	17	3	0.40
R II	37	3	16	4	0.20
R III	40	0	19	1	0.30
R IV	33	7	19	1	0.05
R V	32	8	19	1	0.03
R I–III	40	0	20	0	0.99
R III–V	39	1	20	0	0.31
R I–V	40	0	20	0	0.99
L I	38	2	17	3	0.25
L II	35	5	16	4	0.46
L III	35	5	18	2	0.76
L IV	29	11	16	4	0.510
L V	32	8	19	1	0.032
L I–III	38	2	20	0	0.14
L III–V	36	4	20	0	0.035
L I–V	38	2	20	0	0.147

Table 3. A comparison of BAEP studies in the literature.

	L_I	L_{III}	L_V	$L_{I–III}$	$L_{III–V}$	$L_{I–V}$	A_I	A_{III}
Aydogan et al. (6)	N	↑(bilaterally)	↑(right)	↑(bilaterally)	N	N		
Nikiforidis et al. (2)	↓	N	N	↑	N	N		
Özüer et al. (3)	N	N	N	N	N	N	N	N
Hong et al. (1)	↓	N	N	↑	N	↑		
Shalaby et al. (7)	N	N	N	N	N	N		
Elsaied et al. (5)	N	↑(left)	N	↑(left)	↑ (right)	↑(left)		
Hong et al. (1)	↓	↑	N	↑	N	N		
Our study	N	N	N	N	N	N		

L: Latency, A: amplitude.

was not observed between other thyroid parameters (TSH, free T4, thyroglobulin) and BAEP parameters. Neither thyroid parameters nor BAEP parameters were significantly correlated with the duration of the disease, age of patients, or age at disease onset.

4. Discussion

The results of several studies on audiological abnormalities in vitiligo were controversial. In some of these studies, hearing abnormalities were evaluated by pure-tone audiometry (4,6,7). In other studies, BAEPs were measured

to examine auditory pathway abnormalities (2,3). Tosti et al. detected sensorineural hypoacusis in 16% of 50 patients with vitiligo (4). Sharma et al. found that the hypoacusis rate was significantly higher in the vitiligo patients than the control group (17). In Nikiforidis et al.'s study, 12.3% of vitiligo patients had audiological abnormalities (2).

BAEP studies performed in vitiligo patients demonstrated various results in the literature. The results of those studies are shown in Table 2. Elsaied et al.'s study showed a statistically significant increase both in left ear third latency (P = 0.04) and in interpeak I–III and interpeak I–V latencies (respectively, P = 0.001 and 0.04). In addition, a statistically significant increase in right ear III–V IPL was noted in the vitiligo patients compared to the control group (P = 0.02) (5). In Hong et al.'s study, a significant decrease in peak I latency and a significant increase in third peak latency and I–III IPL were seen in the patients with vitiligo (1). It was postulated that a decrease in first peak latency might be due to decreased number or activity of inner ear melanocytes in vitiligo patients (1). Nikiforidis et al. demonstrated that there were more statistically significant decreases in first peak latency and more statistically significant increases in I–III IPL in patients with vitiligo than the control group. The authors argued that a decrease in first peak latency might be related to a decrease in numbers of melanocytes in the inner ear and an increase in I–III IPL might be related to abnormal synaptic activity and transmission from the cochlear nerve towards the superior colliculus and delayed action potential synchronization in the nucleus (2).

In a few studies, pure-tone audiometry and BAEP results were assessed together. In Özüer et al.'s study, 4% audiological problems were detected in their patient group, but no statistically significant differences in latency, IPL, or amplitudes were detected between the patients with vitiligo and the control group (3). In Aydogan et al.'s study, sensorineural hypoacusis was detected with audiological tests in 14% of the patients with vitiligo. Increased third peak latency and I–III IPL in both ears and increased V peak latency in the right ear were detected in the patients with vitiligo compared to the control group. There were no differences in other latencies or IPLs between the groups (6). In Shalaby et al.'s study, no statistically significant differences in BAEP results or pure-tone audiometry results were detected among the vitiligo and control groups (7).

In our study, the frequencies of prolonged latency and IPL and of decreased amplitudes were higher in the vitiligo group than the control group. No statistically significant differences in mean values of BAEP parameters were detected in our study; these findings were similar to the previous studies performed by Özüer et al. and Shalaby et al. (3,7). However, the number of abnormal results in BAEP parameters including left V, left III–V, right IV, and right V was statistically higher in the patient group than the control group. These waves may indicate the electrophysiological abnormalities between the olivary nucleus in the pons and inferior midbrain. Differences between studies may be related to the complex and multifactorial pathogenesis of vitiligo, residual melanocyte numbers in the inner ear, personal sensitivity, and coexistence of other immunological diseases.

Vitiligo is an autoimmune-mediated disease. The frequency of autoimmune diseases including thyroid disease, pernicious anemia, Addison disease, chronic urticaria, alopecia areata, psoriasis, asthma, systemic lupus erythematous, multiple sclerosis, myasthenia gravis, inflammatory bowel disease, scleroderma, Sjögren syndrome, and type I diabetes mellitus is higher in patients with vitiligo than the normal population (18–20). The most common autoimmune disease accompanied by vitiligo is thyroid disease. In several studies, autoimmune thyroid disease and abnormal thyroid tests are more frequently seen in patients with vitiligo than control groups (12–14).

Anti-TPO is a sensitive marker for early diagnosis of subclinical autoimmune thyroid disease, evaluation of immunotherapy response, and detection of high-risk individuals for autoimmune thyroid disease (21). In our study, the presence of thyroid autoantibodies (anti-TPO and anti-TGA) was statistically significantly higher in the patients with vitiligo than the control group (P = 0.042), compatible with previous studies (12,13,22).

Hashimoto thyroiditis (HT) is one of the most common autoimmune endocrine disorders and is characterized by the presents of antibodies against anti-TPO and/or antibodies against thyroglobulin (23,24). Hashimoto encephalopathy is a rare but well-known complication of HT and is associated with elevated antithyroid antibodies. HT presents with various neurological manifestations such as altered mental status, agitation, refractory seizures, status epilepticus, or cognitive decline (23–25). Although the exact pathogenesis is still unknown, elevated antithyroid antibodies can affect the nervous system seriously (26,27). Hearing pathways are also sensitive pathways of the central nervous system and are vulnerable to various metabolic and toxic disorders (23,27). Gawron et al. showed that there was a positive correlation between the blood concentration of anti-TPO and the extent of the disturbances in the central part of the hearing organ. They pointed out the possible presence of subclinical Hashimoto encephalopathy affecting the central part of the auditory organ (28). Sharma et al. assessed the auditory pathway by BAEPs in 25 newly diagnosed patients with subclinical hypothyroidism and healthy sex- and age-matched controls. The prolongation of wave V in BAEPs of both ears suggested that the central auditory pathway

is affected significantly in subclinical hypothyroid patients (29). Since antithyroid antibodies can affect other parts of the nervous system, they may affect hearing pathways, as well. BAEP parameters are a sensitive way to determine hearing system function. The correlation between BAEP parameters and antithyroid antibodies can give an idea about their effects on hearing pathways.

In this study, we also assessed the correlation between thyroid gland-related parameters indicating autoimmunity and BAEP parameters. To date, this correlation was not studied before. The correlation of anti-TPO and BAEP results showed that when anti-TPO increased, right III decreased in 34.8% of the measurements (negative correlation; statistically significant ($P < 0.05$)). There were also negative correlations between anti-TPO and right V, right I–III, right IV, left I–V, and left IV (respectively 38.6%, 37.5%, 54.1%, 33.2%, and 44.3%), which were statistically significant ($P < 0.05$). There were negative correlations between anti-TGA and BAEP parameters including right I–III, right IV, and left III (respectively $R = -0.336$, -0.353, and -0.331), which were statistically significant ($P < 0.05$). There was a statistically significant negative correlation between serum T3 and left III–V parameters (31.6%; $P < 0.005$). Lastly, no statistically significant negative or positive correlations among other thyroid parameters including TSH and serum T4 and BAEP parameters were detected in this study.

The presence of a correlation between elevated anti-TGA and anti-TPO levels and BAEP parameters demonstrates that abnormal BAEP parameters may be related to an autoimmune-mediated mechanism. Absence of a correlation between BAEP parameters and TSH and free T3 levels, which are not related to autoimmunity, is also a supportive finding that abnormal BAEP parameters and also hearing systems may be related to autoimmune-mediated mechanisms in patients with vitiligo.

Based on our results, melanin may play an important role in the formation of the hearing system, maintenance of hearing function, and modulation of auditory stimulation in the inner ear. To date, the correlation between autoimmunity and BAEP response was not studied previously. The significant correlation between autoimmune antibodies and BAEP responses may indicate the presence of an underlying autoimmune mechanism. However, multicenter studies are warranted to investigate the effects of vitiligo on hearing disturbances and the auditory system.

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