

Evaluation of the Clinical and Sociodemographic Features of Turkish Patients with Vitiligo

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ABSTRACT Vitiligo is an acquired, pigmentary skin disorder that affects about 0.1-4.0% of the population. In this study, we aimed to investigate the disease features such as age of onset, disease duration, clinical and sociodemographic characteristics, and laboratory parameters of patients with vitiligo. A hundred patients who were in follow-up for vitiligo between the period of June 2013 and May 2014 were included in the study. The clinical features and laboratory parameters were retrospectively obtained from the records of the patients. The mean age was 34.9 ± 16.8 years. The most common clinical types were focal and acrofacial. Facial involvement was the most common localization. Forty-five (45%) patients had an associated systemic disease. Autoimmune thyroid disease, essential hypertension, and alopecia areata, which were observed in 28%, 8%, and 5% of patients, respectively, were the most common associated diseases. Twenty-one percent of the patients had low ferritin levels, 20% had low iron levels, 12% had low vitamin B12 levels, and 1% had low folic acid levels. The prevalence of anti-TG (anti-thyroglobulin) and anti-TPO (anti-thyroid peroxidase) antibodies were found 17% and 27% of the patients, respectively. We found that the clinical characteristics of vitiligo in our patients were similar to those in other studies. We observed laboratory abnormalities and accompanying diseases associated with vitiligo. Therefore we conclude that laboratory examinations including thyroid antibodies and regular follow-up of these patients are essential.

KEY WORDS: vitiligo, sociodemographic characteristics, autoimmunity, thyroid antibodies

INTRODUCTION

Vitiligo is a disorder characterized specifically by melanocyte destruction and clinically by depigmented macules which can either be hereditary or acquired (1). Its prevalence is approximately 1% (2). In Turkey, the frequency of vitiligo is reported as 0.15-0.32% (3). Although can be found in every age group,

50% of the cases are younger than 20 and 70-80% of the cases are under the age of 30 (4). The etiology of the disease is not clear, but genetic predisposition, autoimmunity, and toxic metabolites are thought to be responsible for the pathogenesis of the disease (5).

In the literature there are several studies evaluating the relation of vitiligo with other autoimmune disorders, laboratory parameters, clinical features of different age populations, and genetic predisposition. In this study, our aim was to evaluate the age of onset of the disease, family history, the extent of the involvement, sex, as well as the association with other disorders in patients with vitiligo, in order to report the clinical properties and laboratory parameters in Turkish population.

PATIENTS AND METHODS

The data of the 100 patients with vitiligo treated in our clinic between June 2013 and May 2014 were retrospectively evaluated. Age, sex, type of the disease, distribution of the lesions, the age of onset, family history (in the first, second and third-degree relatives), accompanying diseases, systemic and topical treatments, and laboratory parameters are recorded for all of the patients. The patients who had new lesions or had extending lesions in the last 3 months were reported as "active", and the patients showing no difference in their lesions were reported as "stable".

According to their clinical involvement, patients were subdivided into six groups: focal, acrofacial, generalized, segmental, mucosal, and universal. The levels of hemoglobin and iron, vitamin B12, folic acid, anti-thyroglobulin antibody (anti-TG), anti-peroxidase antibody (anti-TPO), thyroid stimulating hormone (TSH), free thyroiodothyronine (fT3), free thyroxine (fT4), hepatitis B antibodies (anti-HBV), hepatitis C antibody (anti-HCV), and anti-HIV antibodies were recorded as the laboratory parameters.

Regarding the descriptive statistics of the data, mean, median, standard deviation, minimum-maximum, ratio, and frequency levels were used. The distribution of the parameters was controlled by the Kolmogorov-Smirnov test. For the analysis of the quanti-

tative data, Kruskal-Wallis, Mann-Whitney U test, and independent samples t-test were used. Chi-square test was used for quantitative analysis, and for the data for which the chi-square test was not appropriate, the Fisher's exact test was used. The results with *P* values of <0.05 were defined as statistically significant. The SPSS 22.0 (Armonk, NY: IBM Corp) program was used for the analysis of the data. This study has been approved by the research ethics committee of the Okmeydani Training and Research Hospital.

RESULTS

A hundred patients with vitiligo were recruited in our study. Forty-nine of the patients were women and 51 were men. The age of the patients were between 3 and 78 (mean age (\pm standard deviation): 34.9 \pm 16.8). Twelve (12%) of the patients were children (\leq 15 years of age) and 84 (84%) of them were adults (\geq 15 years of age). The age of onset of the disease had a wide range, between 2 and 73 (mean age of onset: 30.2 \pm 16.9). The mean age of onset was 30.0 \pm 17.4, 30.3 \pm 16.6 in female and male patients, respectively. The duration of the disease ranged between 1 month and 39 years (the mean duration: 4.9 \pm 6.7 years). The age of onset of the disease, the duration of the disease, the distribution of the involvement types, the family history, the accompanying diseases, and the ratio of autoimmune disorders showed no statistically significant difference between the sexes (*P*>0.05). A positive family history was present in 27% of the patients (in 11% of them in first-degree relatives, in 12% of them in second-degree, and in 10% in third-degree relatives). The disease was active in 82% of the patients and stable in 18%.

The distribution of the lesions was as follows: facial involvement 72%, upper extremities 69%, lower extremities 64%, trunk 39%, and anogenital region 31%. The clinical types were focal in 39%, acrofacial

Table 1. Clinical features and demographic characteristics of patients with vitiligo

	Women (n)	Men (n)	Women (%)	Men (%)	<i>P</i>
Age of onset (mean \pm SD (range))	30 \pm 17.4 (4-71)	30.3 \pm 16.6 (2-73)			0.928
Disease duration (mean \pm SD (range))	5.7 \pm 7.9	4.1 \pm 5.1			0.512
Forms of disease					
Focal	22	17	43.1	34.7	0.4
Generalized	15	11	29.4	22.4	
Acrofacial	12	19	23.5	38.8	
Universal	2	2	3.9	4.1	
Family history	14	13	27.5	26.5	0.917
Associated autoimmune disorders	20	15	39.2	30.6	0.367

*SD: Standard deviation

in 31%, generalized in 26% and universal in 4% of the patients. The clinical features of the patients are shown in Table 1.

Forty-five percent of the patients had an accompanying systemic disease. The most common disease was autoimmune thyroid disorder (28%) and the others were essential hypertension (8%) and alopecia areata (5%) (Table 2). The frequency of autoimmune diseases was 35%. Systemic diseases were found in 38.4% of the patients with generalized vitiligo and in the 17.9% of the patients with focal vitiligo. Four percent of the patients had a malignancy. These malignancies were cranial tumor, leukemia, and breast cancer.

The age of onset of the diseases did not show a significant correlation with the type of the involvement, family history, or the presence of an autoimmune disorder ($P>0.05$).

Focal disease had a significantly slower disease course in comparison with the generalized, acrofacial, and universal forms ($P=0.001$). Between the generalized, acrofacial, and universal forms, the difference in the duration of the disease was not statistically significant ($P>0.05$).

In our study, the possibility of a patient having at least one positive thyroid antibody was found to be 36%. Positive anti-TPO was found in 27% of the patients, and 17% of them were anti-TG positive (Table 3). The positivity of the autoantibodies had the same frequency in both sexes. Among these patients, 14% of them had focal, 10% had acrofacial, 9% had generalized, and 1% had universal vitiligo. Twenty-eight percent of patients with positive autoantibodies had autoimmune thyroiditis, and 15% of these patients were hypothyroid while 85% were euthyroid. Autoimmune thyroiditis was present in 23% of the patients with generalized vitiligo and in 12% of the patients with focal vitiligo.

Table 2. Vitiligo-associated diseases

	n (%)	Men/Women
Autoimmune thyroid disorder	28	10/18
Essential hypertension	8	3/5
Alopecia areata	5	2/3
Malignancy	4	1/3
Asthma	3	1/2
Type 2 diabetes mellitus	2	0/2
Psoriasis	2	1/1
Heart failure	2	0/2
Immune thrombocytopenic purpura	1	1
Pernicious anemia	1	1/0
Others	6	

When other laboratory parameters were evaluated, 21% of the patients had lower ferritin, 12% had lower B12, and 1% had lower folic acid levels. Three percent of the patients had positive viral markers (2 had anti-HBV, 1 had anti-HCV positivity). The frequency of anemia was 15% (Table 3).

Fifty two percent of the patients were given local treatments (topical steroids (31%), pimecrolimus (13%), tacrolimus (10%), herbal therapies (4%)) while 14% had systemic treatments (Narrow band ultraviolet B (UVB) and psoralen combined with ultraviolet A PUVA (13%), cyclosporine (1%)).

DISCUSSION

Vitiligo is a pigmentation disorder characterized by depigmented macules due to melanocyte destruction which affects the skin, hair, and mucosa. Patients may have emotional stress or social stigmatization due to cosmetic reasons (6,7).

The incidence of vitiligo differs among countries. In Denmark the incidence of the disease is 0.36%, in Lebanon it is 0.33%, and in China the incidence was reported as 0.093% (8,9). The highest incidence was found in Nigeria with 6% (6).

Although vitiligo can be found in both sexes, in some studies it was reported to be more common in women due to cosmetic reasons (6,8). In our study, male and female ratios were quite similar, and this finding is consistent with the findings of Lu *et al.* and Gönül *et al.* (9,10)

The onset of vitiligo has varied among different studies. Results of a study by Gönül *et al.* showed that 29% of their patients were aged under 30 (10). Pradhan *et al.* reported that the majority of the patients had onset of the disease under the age of 25 (11). In our study, 20% of our patients had onset of the disease before 20 years of age.

In Sigh's vitiligo study, the ages of the patients

Table 3. Laboratory findings of patients with vitiligo

Laboratory parameters	n (%)
Decreased ferritin level	21
Decreased iron levels	20
Decreased vitamin B12 levels	12
Decreased folate levels	1
Anemia	15
Positivity of viral markers	3
Positivity of anti-TPO	27
Positivity of anti-TG	17
Positivity of thyroid antibodies (anti-TPO or anti-TG)	36

ranged between 10 months and 58 years (12); in Onunu's study, the age range was between 9 months and 80 years (6). Lu *et al.* reported that 69% of the patients were between 15 and 64 years of age (9). Gönül *et al.* reported the mean age for the patient population as 37.4 (10). In our study, the age-range was between 3 months and 78 years (the mean age was 34.9). Our findings were similar to previous studies.

Vitiligo has been observed in the pediatric population as well. In a study performed in India, 625 pediatric patients were recruited and the mean age at the time of diagnosis was reported as 6.2; the most common form of vitiligo was generalized vitiligo (13). In our study, there were 12 (12%) patients under the age of 15, and the most common form was focal vitiligo (8%).

In our study, 82% of the patients had the "active" form of the disease. Zhang *et al.* analyzed 6516 patients, and the active form of the disease was reported in the 32% of the patients, whereas in Gönül *et al.* found the ratio to be 44% (10,14).

More than 30% of vitiligo cases are known to have an affected relative and 21% to have an affected first-degree relative (15). Previous reports have reported the incidence of a family history at between 12% and 36% of patients (11). Handa *et al.*, similar to our findings, found that 11.5% of the patients had a family history in first-degree relatives (13). In Japan, family history was observed in 3.4% (16). In our study, the overall family history in first, second, and third-degree relatives was recorded in 27% of patients. This higher ratio may be due to the fact that consanguineous marriages are common in our country.

Where clinical forms are concerned, in Japan the most common forms were generalized, focal, and segmental, whereas the generalized form was most common in Libya (12,16). Lu *et al.* reported 28% generalized, 26% focal, and 12.4% acrofacial vitiligo (9). In the present study, in contrast to previously published reports, focal vitiligo was the most common clinical type, followed by acrofacial and generalized forms. This can be explained by more patient awareness of the cosmetic disfigurement, therefore making them more likely to seek treatment.

Gönül *et al.* reported that the most common site of involvement was the face and the upper extremities (10). Yoshida *et al.* reported higher frequencies of face, chest, and abdomen involvement (16). In our study, the most common lesions sites were the face and the upper extremities. The higher incidence of facial involvement is thought to be due to sunlight exposure and physical trauma, which may play role in the pathogenesis of the disease.

Vitiligo has been reported to be accompanied by pernicious anemia, Addison's disease, diabetes mellitus, myasthenia gravis, scleroderma, rheumatoid arthritis, alopecia areata, autoimmune thyroid diseases, and many others (17). Most of these disorders are autoimmune in origin. There were also some changes in humoral and cellular immunity in molecular studies of vitiligo, which are said to play role in the disease pathogenesis. In one of the studies from Turkey, there were IgG and C3 deposition in the basal membranes and keratinocytes of the vitiligo lesions, which are consistent with autoimmunity (18). In Zheng's study, more common autoimmune disorders seen in vitiligo patients were rheumatoid arthritis, hyperthyroidism, hypothyroidism, alopecia areata, and chronic urticaria. In familial vitiligo cases, diabetes, thyroid disorders, and rheumatoid arthritis were common (14). In our study, thyroid disorders, essential hypertension, and alopecia areata were the most common accompanying disorders. In familial vitiligo cases the most common disorders were autoimmune thyroid disorder and alopecia areata. Gönül *et al.* reported that the most common systemic disorders were autoimmune thyroid disease, diabetes mellitus, and essential hypertension (10). In recent studies, some evidence has shown that T lymphocytes play a role in the etiology of essential hypertension. Guzik *et al.* proved that angiotensin II-induced hypertension never develops in rats which do not have lymphocytes. Researchers also noted that the periaortic tissue showed lymphocytic infiltration in cases of angiotensin II-induced hypertension, and that local cytokine production may play role in the change of the vascular reaction (19). All these results show that essential hypertension may also be an autoimmune disorder just like vitiligo. Further studies are needed to prove this hypothesis.

Akay *et al.* reported that 55% of vitiligo patients had autoimmune disorders (Hashimoto thyroiditis 31.0%, alopecia areata 12.5%, pernicious anemia 8.7%, and diabetes mellitus 2.5%) (20). In our study, 35% of the patients had autoimmune disorders (autoimmune thyroid disorder 28%, alopecia areata 8%, psoriasis 2%, pernicious anemia 1%, immunothrombocytopenic purpura 1%).

Thyroid dysfunction and thyroid autoantibody positivity were present in varying amounts in patients with vitiligo (21). Thyroid dysfunction may be sub-clinical or may reach the clinically meaningful grades, and these patients may be diagnosed with Graves' disease, Hashimoto thyroiditis, hypothyroidism, or hyperthyroidism. This finding indicates the need for regularly evaluating these patients by means of thyroid dysfunction and thyroid-related antibodies. It is known that anti-TPO positivity in Turkey is around



7-8% (18). Akay *et al.* (Turkey) found 31% positive anti-TPO in the patient group with vitiligo. Yang *et al.* reported 24.1% positive anti-TPO and 23% anti-TG in their patient population (20,21). In our study, the rate of a patient having at least one positive thyroid antibody was found to be 36%. Thyroid antibodies were most commonly found in patients with focal vitiligo. Twenty-eight percent of these patients having positive autoantibodies had autoimmune thyroiditis, and 15% of these patients were hypothyroid while 85% were euthyroid. Autoimmune thyroiditis was most commonly found in patients with generalized vitiligo.

The frequency of diabetes mellitus was reported as 1-7% in patients with vitiligo. Both of the disorders are associated with HLADR3 and HLADR4. T lymphocytic stimulation against pancreas islet cells and therefore firing of inflammatory response were attributed to the pathogenesis of type 1 diabetes mellitus. Long-lasting diabetes mellitus is thought to increase the release of antigenic materials, and this may lead to melanocyte destruction and inhibition of melanogenesis; this whole process may play a role in the pathogenesis of vitiligo. In our study, the frequency of type 2 diabetes mellitus was found to be 2% (22).

Free radicals may be toxic for melanocytes and may cause harm. This mechanism may also play role in the pathogenesis of vitiligo (23). Nitric oxide is an enzyme causing melanocyte loss. Iron binds to the cofactor of this enzyme and therefore decreases its activity. In vitiligo cases, repigmentation is observed after the treatment of iron-deficiency anemia. This finding has induced researchers to evaluate the iron and ferritin depots in vitiligo cases (24). A Turkish study performed by Mansur *et al.* found no significant difference between the patient and control group in serum iron and ferritin (24). Gönül *et al.* found a decrease in ferritin and iron levels by 20.4% and 27.2%, respectively (25). In our study, these levels were found to be 21% and 20%, respectively. There are studies evaluating vitamin B12 and folic acid levels in patients with vitiligo. Gönül *et al.* found vitamin B12 deficiency in patients with vitiligo to be 6.8%, whereas folic acid deficiency was 4.5% (25). However, when the control and patient groups were compared, there was no significant difference reported. Vitamin B12 deficiency was 12% and folic acid deficiency was 1% in our patients. We did not have a control group and therefore we cannot reach further conclusions on this subject.

There are studies showing that hepatitis viruses play a role in some autoimmune diseases such as lichen planus, mixed cryoglobulinemia, and psoriasis.

In recent studies, hepatitis C virus (HCV) seropositivity was reported in some patients with vitiligo (26). A hundred and two vitiligo cases were evaluated by means of HCV seropositivity; anti-HCV was reported to be positive in 0.98% of the cases in a Turkish study (27). Our findings are consistent with this study, since anti-HCV positivity was only 1%. Akcan *et al.* evaluated hepatitis B (HB) prevalence in patients with vitiligo as well as hepatitis B surface antigen; anti-HBs positivity was found to be less in the patient population in comparison with the healthy controls (28). Hepatitis B surface antigens were positive in one patient in our study. These results indicate that hepatitis viruses do not play a role in the pathogenesis of the disease.

CONCLUSIONS

Vitiligo is a multifactorial disorder in which genetic and environmental factors play a role. In our study, we found that the prevalence of vitiligo was at a similar ratio in both sexes, and the most common form of vitiligo was the focal form. Family history of the disease was frequently found in our patient group. In some of our patients, accompanying diseases such as autoimmune thyroid disorders, hypertension, and alopecia areata were found, and furthermore some of the laboratory parameters were at abnormal values. Therefore it can be said that vitiligo is not only a cosmetic issue. In our opinion, clinicians should pay extra attention to patients with a positive vitiligo family history and should inform them about the possible harmful effects of sun-exposure as well as monitor those patients, especially with thyroid autoantibody testing and also with other laboratory tests.

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