Journal of Pigmentary Disorders
ISSN: 2376-0427

Attwa et al., Pigmentary Disorders 2014, 2:1
DOI: 10.4172/2376-0427.1000154

Research Article Open Access

Vitiligo and Associated Autoimmune Diseases in Zagazig University Hospitals, Sharkia Governate, Egypt

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Abstract

Although the pathogenesis of vitiligo is not yet fully understood, the autoimmune hypothesis is the most commonly accepted. The aim of this study was to study the frequency of autoimmune diseases in a group of Egyptian patients with vitiligo compared with control. This study involved 50 Egyptian patients with vitiligo and 50 healthy subjects as control group. Patients should be made aware of signs and symptoms that suggest the onset of thyroid dysfunction, diabetes, or other autoimmune disease. If signs or symptoms occur, appropriate tests were performed. Screenings for thyroid disease were through evaluation of thyroid antibodies (anti-thyroidperoxidase, anti-thyroglobulin antibody), serum thyrotropin (TSH), free tri-iodothyronine (T3) and free thyroxine (T4). Screening for diabetes was done with fasting blood glucose or glycosylated hemoglobin testing. A complete blood count with indices helped rule out anemia. Antinuclear antibody screening was also done. Screening for celiac disease, IgA anti-glutaminase antibody was measured. The frequencies of autoimmune disorders were significantly elevated in vitiligo patients: vitiligo itself, autoimmune thyroid disease (particularly hypothyroidism), alopecia areata, pernicious anaemia, adult-onset type 1 diabetes mellitus, psoriasis and probably inflammatory bowel disease. These associations indicate that vitiligo shares common genetic aetiologic links with these other autoimmune disorders.

Keywords: Vitiligo; Autoimmune diseases; Anti–thyroidperoxides; Anti–thyroglobulins

Introduction

Vitiligo is an acquired depigmenting disorder. Vitiligo may be associated with other autoimmune diseases, especially thyroid disease and diabetes mellitus. Other associated autoimmune diseases include pernicious anemia, Addison disease, and alopecia areata [1]. Different theories regarding its pathogenesis have been put forward, autoimmunity being the most popular one. The latter is based mainly on the association of vitiligo with known autoimmune diseases and the presence of organ specific antibodies in affected patients [2]. Another common finding in support of this hypothesis is that vitiligo often responds to immuno-suppressive treatments. The mechanisms of immunity are humoral (antibody-mediated), cell-mediated, or mediated by cytokines. Auto- antibodies and their respective target cells are also relevant to the pathogenesis of vitiligo [3].

Thyroid functional disorders and autoimmune thyroid diseases (ATD) have been reported in association with vitiligo, and it seems that the incidence of clinical and subclinical thyroid involvement is more common in vitiligo patients than healthy subjects [4].

Hashimoto thyrioditis and Graves' disease are the most important autoimmune thyroid diseases that characterized by elevated serum antibodies directed against thyroid-specific antigens like thyroperoxidase (TPO) and thyroglobulin (TG). Patients with non-segmental vitiligo display an increased presence of elevated anti-TPO antibodies and show a high prevalence of ATD. Therefore, the presence of elevated anti-TPO antibodies may serve as a useful clinical tool in euthyroid subjects with vitiligo to identify patients at risk for thyroid disease [5].

Vitiligo often precedes the clinical manifestations of thyroid gland dysfunction [6,7]. Thus, screening of patients with vitiligo for thyroid function and anti-thyroid antibodies to diagnose early changes in the function of this gland becomes relevant and necessary [8].

Both the lichen planus and psoriasis occurred on lesions of the preceding vitiligo vulgaris. The potential mechanisms for association of these three dermatoses, may consider the Koebner phenomenon related to the photo damage causing initiation of lichen planus and psoriasis over vitiliginous skin which supports their pathogenic relationship [1,9].

There may be a relationship between celiac disease and vitiligo. This may indicate a common basic autoimmune mechanism that is an explanation for few case reports that gluten free diets were effective in the treatment of vitiligo patients [10].

Coexistence of systemic lupus erythematosus and vitiligo has been infrequently reported. However, cases of vitiligo coexisting with discoid lupus erythematosus (DLE) have been much rarer [11]. There have been rare published cases of DLE with other autoimmune cutaneous and systemic disorders. Sharma et al. [12] described a 36 years old female patient with DLE lesions on the face and hands with coexistence of lip-tip vitiligo and hypothyroidism which supported their autoimmune pathogenic relationship.

The aim of this study was to study the frequency of autoimmune diseases in a group of Egyptian patients with vitiligo compared with control.

Patients and Methods

This study was conducted in the Dermatology, Venereology and Clinical Pathology Departments, Faculty of Medicine, Zagazig University Hospitals, in the period from December 2013 to August 2014. The research protocol was approved by local ethics committee and all subjects provided written informed consent.

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Received October 31, 2014; **Accepted** November 03, 2014; **Published** November 05, 2014

Citation: Attwa E, Nofal A, Khater MH, Gharib K, Khalifa N (2014) Vitiligo and Associated Autoimmune Diseases in Zagazig University Hospitals, Sharkia Governate, Egypt. Pigmentary Disorders 2: 154. doi:10.4172/2376-0427.1000154

The study included 50 patients with different clinical forms of vitiligo diagnosed according to the clinical picture and 50 clinically free subjects as a control group. Patients were questioned about the age at onset, the duration of the disease, and the personal and familial medical history of vitiligo, autoimmune thyroid diseases, rheumatoid arthritis, type 1 diabetes mellitus, psoriasis, pernicious anemia, SLE, Addison's disease, alopecia areata, and other autoimmune diseases. Multi-specialist medical evaluations were carried out to confirm the diagnoses in some patients and family members.

Patients with thyroid surgery, those on anti-thyroid medications or with other causes of leukoderma and children less than 6 years of age were excluded from the study.

General examination was performed for all the patients and controls with emphasis on the signs of hyperthyroidism (fine hair, thin skin, muscle weakness, tachycardia, tremors, stare and lid lag), signs of hypothyroidism (growth retardation, deep hoarse voice, dry coarse skin and bradycardia) and other autoimmune diseases. If signs or symptoms occur, appropriate tests were performed.

Determination of thyroid auto antibodies; anti-TPO and anti-TG using enzyme linked immunosorbent assay (ELISA). Anti-TPO and anti-TG levels in the serum samples were determined by using Kit (Orgentec diagnostika Gmb, 55129 Mainz- Germany) [13,14].

Determination of thyroid hormonal profile; free thyroxine (f.T4), free tri-iodothyronine (f.T3) and thyrotropin (TSH) levels in the serum samples were determined by using Aeon-Bind ELISA kit (Monobind Inc. Lake Forest, CA 92630, USA) [15].

A complete blood count, fasting blood glucose or glycosylated hemoglobin, anti-nuclear antibody, double-stranded DNA antibody were detected.

Serum IgA anti transglutaminas (tTG) antibodies were evaluated by the enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Binding site, Minineph R, UK) and values ≥7 IU/l were considered as positive. Serum IgA anti endomysial (EMA) antibodies were evaluated by immunoflourescence assay (IFA). If the level of anti-tTG was <0.1 IU/ml, the total serum IgA level was measured for ruling out IgA deficiency.

Statistical Analysis

Analysis of the data was performed using SPSS computer program (Statistical Package for Social Sciences) version (10.0). Data are summarized as means and standard deviation (±SD). T-test is used for comparison of mean and standard deviation (±SD) of two groups. Qualitative data are presented as number and percentage. Chi-square test is used for association between qualitative data. Fisher exact test is used as recommended when expected cell is less than 5. Correlation coefficient between quantitative values was done. Probability is considered significant when p value equals or is less than 0.05.

Results

Ten (20%) of the patients had positive family history. Thirty-one patients (82.0%) had generalized, 5 (10.0%) had Acrofacial, 2 (4%) had segmental vitiligo and the last two (4%) had focal vitiligo. There was no statistical significant difference between patients and controls as regard age and sex (Table 1). Anti-thyroid peroxidase antibody level was detected in (26%) of patients with vitiligo in comparison to (8%) in controls. The difference was statistically significant (p=0.01). Anti-TG was detected in (16%) of patients in comparison to (2%) in the control group. The difference was statistically significant (p=0.01). There was no statistical significant difference between thyroid hormones levels in patients as regard their age (Table 2).

Local examination of thyroid gland of vitiligo patients showed no abnormalities. On general examination, three of them had manifestations of hypothyroidism.

Thyroid function tests of patients revealed that 15 (30%) suffered from hypothyroidism and 4 (8%) suffered from hyperthyroidism. There was a statistically highly significant difference between patients and controls as regard diagnosis of hypothyroidism (P<0.001) (Table 3). There was no statistically difference between vitiligo patients with thyroid dysfunction regarding sex (p=0.72). There were no statistically differences between serum levels of anti-TPO or anti-TG and risk factors (sex, family history, thyroid dysfunction and type of vitiligo) (Tables 4 and 5).

Seven vitiligo patients (14%) were suffered from other autoimmune diseases. One patient was seropositive for both anti Endomysial and anti transglutaminase antibodies. He had highly positive tTG levels: 42.8 IU/l. None of the control group was seropositive for these autoantibodies (P<0.05). Another one patient reported coexistence of vitiligo vulgaris and psoriasis vulgaris on his upper arms. Psoriasis occurred on lesions of the preceding vitiligo vulgaris. Also, one vitiligo patient had pernicious anemia, one patient had adult- onset type 1 diabetes mellitus and three patients had alopecia areata (Tables 6-8).

Discussion

Although the pathogenesis of vitiligo is not yet fully understood, the autoimmune hypothesis is the most commonly accepted. This theory is supported by the clinical association of vitiligo with autoimmune

	Patients (N=50)		Controls (N=50)		Tests of P. Sig.
Age (years):					
X ± SD	30.54 ± 8.24		31.26 ± 6.13		t 0.49 0.62
Range	22-38		25-37		NS
Sex :					
Male No %	8	16.0	6	12.0	X^2=33.56
Female No %	42	84.0	44	88.0	NS

Table 1: Frequency of age and sex of studied vitiligo patients and controls

	Patients (N)(%)	Controls (N) (%)	X^2	P
Anti-TPO			5.74	0.01 Sig.
Normal	37 (74.0)	46 (92.0)		
High	13 (26.0)	4 (8.0)		

The difference is statistically significant.
Table 2: Frequency of anti-thyroid peroxidase activity among patients and controls

	Patients (N) (%)	Controls (N) (%)	X^2	P
Anti-thyroglobulin			Fisher exact	0.01 Sig.
Normal	42 (84%)	49 (98.0)		
High	8 (16%)	1 (2.0)		

The difference is statistically significant.
Table 3: Frequency of anti-thyroglobulin antibody between patients and controls

Hormones	Age	
	r	P
TSH	-0.16	0.126 NS
FT3	-0.18	0.126 NS0.126 0.126 0.21 NS
FT4	-0.04	0.126 NS 0.21 NS0.21 NS 0 0.75 NS

Table 4: The relation between thyroid hormones and age of patients

	Cases (N)(%)	Controls (N)(%)	X^2	P
Thyroid normal	31 (62.0)	50 (100)	23.5	0.001 HS
Hypothyroidism	15 (30.0)	0 (0.0)	17.65	0.001 HS
Hyperthyroidism	4 (8.0)	0 (0.0)	Fisher exact	0.11 NS

Table 5: Frequency of thyroid dysfunction between the groups

	Cases (N)(%)	Controls (N)(%)	X^2	P
Thyroid normal	27 (64.3)	4 (50.0)	0.64	0.72 NS
Hypothyroidism	12 (28.6)	3 (37.5)		
Hyperthyroidism	3 (7.1)	1 (12.5)		

Table 6: Comparison between thyroid dysfunction according to sex of vitiligo patients

	Anti-TPO				X^2	P
	Normal		Elevated			
	No	%	No	%		
Sex					Fischer exact	1 (NS)
Female	31	73.8	11	26.2		
Male	6	75	2	25		
Family history					Fischer exact	1 (NS)
Negative	29	72.5	11	27.5		
Positive	8	80	2	20		
Thyroid function					2.24	0.32 (NS)
Normal	25	80.6	6	19.4		
Hypothyroidism	9	60	6	40		
Hyperthyroidism	3	75	1	25		
Types of vitiligo					3.26	0.35 (NS)
General	29	70.7	12	29.3		
Acrofacial	5	100	0	0		
Segmental	2	100	0	0		
Focal	1	50	1	50		

Table 7: Relation between some risk factors and serum level of anti-TPO

	Anti-TG				X^2	P
	Normal		Elevated			
	No	%	No	%		
Sex					Fischer exact	0.1 (NS)
Female	35	83.3	7	16.7		
Male	7	87.5	1	12.2		
Family history					Fischer exact	0.65 (NS)
Negative	34	85	6	15		
Positive	8	80	2	20		
Thyroid function					1.47	0.47 (NS)
Normal	25	80.6	6	19.4		
Hypothyroidism	14	93.3	1	6.7		
Hyperthyroidism	3	75	1	25		
Types of vitiligo					2.09	0.55 (NS)
General	33	80.5	8	19.5		
Acrofacial	5	100	0	0		
Segmental	2	100	0	0		
Focal	2	100	0	0		

Table 8: Relation between some risk factors and serum level of anti-TG

disorders, the frequent detection of circulating autoantibodies to surface and cytoplasmatic antigens of melanocytes. Furthermore, there are findings of activated T cells in the periphery of actively progressing lesions in some vitiligo patients [16]. Another common finding in support of this hypothesis is that vitiligo often responds to immunosuppressive treatments [3].

Uncu et al. [17] indicated an autoimmune etiology for vitiligo and genes have been identified that cause both vitiligo and autoimmune thyroid disease. However, little data are available on the association of vitiligo and thyroid disease in children.

Thyroid functional disorders and autoimmune thyroid diseases have been reported in association with vitiligo, and it seems that the incidence of clinical and subclinical thyroid involvement is more common in vitiligo patients than healthy subjects [4]. Vitiligo often precedes the clinical manifestations of thyroid gland dysfunction. Thus, screening of patients with vitiligo for thyroid function and anti-thyroid antibodies to diagnose early changes in the function of this gland becomes relevant and necessary [18].

In this study, the mean age of vitiligo patients was 30.54 years. Similar ages were found in a population in Turkey with a mean age of 31.3 years [19]. The mean ages in other studies were 28.67 years, 37.14 years and 28.11 years [8,19]. This is in keeping with the common age of presentation reported in literature as half of the patients with vitiligo present before the age of 20 years and nearly 70-80% before the age of 30 years [20]. However, a study in India reported alter onset of the disease, with a mean age of 55 years [21]. These data reinforced that vitiligo is a disease that occurs at any age.

In this sample, 84% of participants were females. Similar numbers have been documented in another study in which the female population accounted for 65.9% of the sample [19]. However, other authors have established that there is no difference between genders [21,22].

Shoenfeld et al. [23] suggested that the most convincing explanation for female sex predominance remains the hormonal theory. Estrogens are thought to be potent stimulators of autoimmunity whereas androgens seem to be protective in this respect. Indeed, sex hormones clearly influence both the innate and adaptive immune response with a pivotal role for the influence of estrogens. Another explanation, it is possible that this predominance could be due to a major concern of women with aesthetics.

In this study, the most common type of vitiligo was generalized vitiligo and with regard to the site of onset, the upper limbs were the most frequently affected. They were also the most commonly affected site in an Indian study [24]. These data confirmed that the primary site of involvement is sun-exposed areas. As for the type of lesion distribution, vitiligo vulgaris was reported in several studies [8,22,24, 25] except for one, which was conducted with a child population, in which the focal type was the most common [26]. This is probably due to early medical treatment, immediately after the appearance of the first lesion in the child. Similarly to the results of this study, segmental vitiligo showed a low frequency of 5% [25].

We observed presence of family history in 20% of our patients. Other studies reported 10.6% and 9% in their population [19,27]. However, family history ranged from 34% to 38.7% in a study by Laberge et al. [28]. One can speculate that there was a higher frequency of this variable, especially in the study by Laberge et al. [28], because it was conducted in a population in which several family members were affected by vitiligo, and there was also a more thorough investigation of these families.

Thyroid autoimmune disease with hormonal changes was found in 38% (19 of the patients). Of the 19 cases, 78.9% corresponded to hypothyroidism and 21% to hyperthyroidism. The prevalence of the association between vitiligo and autoimmune thyroid diseases with hormonal changes was 22.4% in a study by Nunes and Esser [19] which was similar to that shown by Laberge et al. [28] who described a frequency of 21.4%. Other studies showed rates of 24.1% [7], 21% [6], and 17% [11].

However, data from previous studies showed low prevalence, such as the values reported in a Chinese study that showed an association of 1.36%, 0.6% in Nigeria, 2.6% in Colombia and 3% in a Romanian population [27]. It is noteworthy that in these studies the lower frequency of these diseases may have occurred due to their methodological characteristic, for laboratory tests were requested only when needed, that is, in the presence of symptoms. According to two studies conducted in Brazil, this association was also low or there was no [26,29], but these studies were conducted specifically with pediatric patients.

Nunes and Esser [19] observed a similar distribution of hypothyroidism (80%) and hyperthyroidism (12-13.3%) among cases of autoimmune thyroiditis and the literature showed that it is rare for vitiligo to develop after thyroid disease, and when present, it occurred at rates close to 4% in the population [7]. It is assumed that that in most cases, vitiligo will develop before autoimmune thyroid diseases. These findings, compared to the rate of 10% of autoimmune thyroid diseases in a study of patients without vitiligo, show the high prevalence of autoimmune diseases and vitiligo [30].

In contrary to our study, Daneshpazhooh et al. [8] and Altaf et al. [31] found no significant thyroid dysfunction with vitiligo. These discrepancies may be due to variations in the sample population, small-sized sample and lack of data in medical records and reduced laboratory tests for thyroid parameters.

In this study, anti-TPO antibody was detected in 26% of patients with vitiligo in comparison to 4% in control group, and anti-TG level was detected in 16% of patients with vitiligo in comparison to 2% in control group. Cases showed significantly higher rate of positive anti-TPO and anti-TG when compared to control ($p<0.05$).

In agreement with our results, many studies reported statistically significant increased levels of anti-TPO in vitiligo patients compared with controls in different countries in Australia [32], UK [33], India [34], Greece [7] and Iran [8].

This antibody, historically referred to as the anti-microsomal antibody, is established as a sensitive tool for the detection of early subclinical autoimmune thyroid diseases, follow up of the response to immunotherapy and identification of at risk cases for autoimmune thyroid diseases. So, the diagnosis of AITD in patients with positive anti-TPO antibodies and not in those with exclusively anti-TG antibodies, because anti-TPO antibodies remain the most sensitive test for AITD diagnosis and follow up [35].

Other studies showed elevated anti-TPO and anti-TG antibody in vitiligo patients [36-38]. According to our study, we found no relationship between the presence of thyroid antibodies and the sex, family history, thyroid dysfunction and localization of vitiligo. Daneshpazhooh et al. [8] found that the difference in the prevalence of anti-TPO was significant only in female cases and patients in the age ranges of 18 to 35 years old, findings not previously reported in the literature. In their study, they found no relationship between the presence of anti-TPO antibodies and the extent, duration, age of onset and anatomical location, Kumar et al. [39] in patients with mucosal and early onset vitiligo. Morgan et al. [39] founded autoantibodies especially in generalized vitiligo and Gey et al. [40] founded autoantibodies in patients with long lasting vitiligo.

The results of these studies in addition to the results of our study are in favor of the autoimmune pathogenesis as they showed that vitiligo patients have higher titer of organ-specific thyroid autoantibodies than the healthy control group, denoting that there is a disturbance in the autoimmune system of vitiligo patients.

Celiac disease is a common immune-mediated enteropathy with a prevalence of approximately 1% within the U.S and European populations. The minimum prevalence of gluten sensitivity among the general population of northern and southern Iran is 1:104 [41]. Serum immunoglobulin A- class tissue transglutaminase (TTGA) and Endomysial antibody (EMA) tests play a key role in the diagnostic evaluation of celiac disease. High serologic IgA tissue transglutaminase antibodies (TTGA) are exclusively associated with celiac disease [42].

The relationship between celiac disease and vitiligo is controversial. Some authors have described cases of vitiligo in patients with celiac disease [41,43], but one serological screening study for celiac disease in patients with vitiligo did not show any correlation between these two immunological disorders [44].

On the other hand, improvement of some disorders likes dermatitis herpetiformis [45], psoriasis [46], and even vitiligo [47], in those who were seropositive for celiac auto antibodies, has been reported by gluten free diet.

In the current study, an IgA antibody to endomysium and transglutaminas was detectable in one patient with vitiligo. All control groups were seronegative for these antibodies ($P<0.05$). The age and sex had no significant effect on seropositivity of patients.

Until now, the results of studies about the relationship between vitiligo and celiac disease are controversial. Seyhan et al. [48] in 2011 compared Sixty-one patients (21 children) with vitiligo and 60 healthy volunteers. Eleven patients with vitiligo (18.0%) and 1 control (1.7%) were seropositive for celiac disease [48]. In another study by this author, 9.1% of Fifty-five children and adolescents with celiac disease had vitiligo [49].

A survey of more than 2,600 unselected Caucasian patients with generalized vitiligo and their close relatives found that, the frequency of five autoimmune antibodies were significantly elevated in vitiligo probands and their first-degree relatives. These associations indicate that vitiligo shares common genetic etiologic links with these autoimmune disorders (autoimmune thyroid disease, pernicious anemia, Addison's disease, systemic lupus erythematosus, and probably inflammatory bowel disease) [50].

In contrast, in the same research there was no significant increase in the frequencies of alopecia areata, type 1 diabetes mellitus, multiple sclerosis, myasthenia gravis, psoriasis, rheumatoid arthritis, scleroderma and Sjogren's syndrome, among the vitiliginous patients, suggesting that the diseases do not share the same common susceptibility genes [50].

The seropositivity for celiac disease in vitiligo may show a common genetic basis for these disorders. This may be observed among peoples in some regions of the world. In our study, in other study in Iran and seyhan et al. [49] study in Turkey, the vitiligo patients were more

seropositive, in comparison with the control group, but in Volta [42] study in Italy no seropositivity for celiac disease autoantibodies was found in these patients [42,48].

In conclusion, recent epidermological findings including ours and genomewide association studies support the long-standing hypothesis that vitiligo mainly generalized type involves genetic susceptibility loci shared with other autoimmune diseases. Similar to autoimmune thyroid disease, generalized vitiligo is now believed to be caused by the damage of melanocytes by various cells and antibody-mediated immune mechanisms. Nevertheless, the initiating process has not well been elucidated. Further study is needed to identify the initiating factors inducting generalized vitiligo, autoimmune thyroid disease and other autoimmune disorders.

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