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ORIGINAL PAPER

Vitiligo and Autoimmunity

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Background: Vitiligo is an acquired skin disorder characterized by depigmented maculae resulting from a reduction of the number and function of melanocytes. The etiopathogenesis of the disease is still unclear, but there is evidence that autoimmunity may be involved. **Objective:** The aim of this study was to determine the prevalence and significance of antinuclear (ANA) and thyroid peroxidase (anti-TPO) antibodies in patients with vitiligo and control group. **Methods:** In a prospective case-control study, we compared the frequency of antibodies (ANA and anti-TPO) in 40 patients with vitiligo and in 40 healthy volunteers. **Results:** ANA were positive in 7 (17%) patients, which was insignificantly higher than control group, 2 (5%). Anti-TPO were positive in 11 (27%) patients. In control group, only two subjects (5%) had positive anti-TPO. Compared with the control group, the frequency anti-TPO were significantly higher in those with vitiligo ($p<0.05$). **Conclusion:** Our findings show a significant association between vitiligo and thyroid autoimmunity, and that tests to detect anti-TPO are useful markers in patients with vitiligo. In contrary, ANA seems to have limited diagnostic relevance in routine clinical practice. Additional studies of a wider sample are warranted to confirm these findings and allow a detailed analysis. Key words: vitiligo, autoimmunity, antinuclear antibodies, thyroid peroxidase antibodies

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1. INTRODUCTION

Vitiligo is an acquired disorder of melanin pigmentation that affects approximately 0.5-2% of the population (1). It is characterized by macular depigmentation of varying sizes or shapes with a tendency to progress. Lesions enlarge centrifugally and can appear on any body sites, including mucous membranes. Depending on the extent of the lesions, vitiligo can be classified into two main categories: generalized and localized. Although several theories have been proposed to explain the loss of melanocytes in vitiligo the etiopathogenesis of the disease is still unclear. The clinical association with autoimmune disorders and organ specific antibodies indirectly support the idea of an autoimmune pathogenesis of the disease (2, 3). Furthermore, many patients with vitiligo have serum autoantibodies and circulating auto reactive T cells directed against melanocytes and there are findings of activated T-cells in the periphery of actively progressing lesions in some vitiligo patients (3, 4).

In the past, several authors described an association of vitiligo with autoimmune disorders and the presence of different tissue autoantibodies. A review of the literature showed large differences in the results. Therefore, the aim of our study was to investigate the prevalence and significance of antinuclear and thyroid peroxidase antibodies in patients with vitiligo and control subject, and also to assess the difference between the localized and generalized form of the disease.

2. PATIENTS AND METHODS

The study included 40 patients with vitiligo, 20 female and 20 male, median age 34.67 (±14.74) years. Of them, there were 12 (30%) patients with generalized vitiligo and 28 (70%) patients with localized form of disease. A detailed history and examination were taken in all study subjects, including patients age, age at onset, duration of disease, associated diseases, and the extent and severity of disease. The diagnosis of vitiligo was made on clinical grounds. Skin biopsy was performed in selected cases. Patients with depigmenting disorders other than vitiligo were excluded. The control group consisted of 40 volunteers, 26 female and 14 male, median age 39.75 (±15.86) years. Blood samples were taken and a physical examination was performed. All subjects gave their informed consent in accordance with the requirements of the institutional Ethics Committee.

Anti-nuclear antibodies, ANA and thyroid peroxidase antibodies, anti-TPO were measured in all subjects. For screening and semi-quantitative determination of ANA in serum specimens we used NOVA Lite HEp-2 im-

munofluorescence kit. All results were interpreted using determined fluorescence grade as 4+; 3+; 2+, + and negative. Serum levels of anti-TPO (borderline value: 34 IU/ml) were measured by use of electrochemiluminiscence immunoassay (ECLIA) according to standard protocols (COBAS, Roche Diagnostics GmbH, Germany). The upper limit of autoantibody was determined by the laboratory.

Statistical analysis was carried out by frequencies of positive or negative results of ANA and anti-TPO (IU/ml). The frequencies of positive or negative laboratory values (ANA and anti-TPO) were compared between groups using χ^2 test. Statistical significance was set at $p<0.05$.

Statistical analyses were performed using MedCalc for Windows, version 12.2.1.0 (MedCalc Software, Mariakerke, Belgium).

3. RESULTS

We performed a cross-sectional study in 40 consecutive patients with vitiligo and 40 age- and sex-matched controls. Demographic data of patients and controls are shown in Table 1. The mean (SD) age of the patient and control groups was 34.68 (±14.75) and 39.75 (±15.87) respectively (p=0.1613).

The age of onset of the disease ranged from 6 to 57 years, with a mine age of 31.26(±14.22) years. In 11 cases (27.5%) the onset was at 20 years or earlier. The mean duration of vitiligo was 40.98 (±41.65), ranged from 2 to 144 months. Twelve patients had generalized, and twenty eight patients had localized vitiligo (Table 2).

We analyzed differences in the frequencies of subjects with positive detectable values of ANA between groups (Table 3). In the vitiligo group there were 7 (17%) patients with positive findings of ANA and the control group, only 2 (5%). No significant association between clinical features of the disease and ANA was detected. ANA were statistically associated with a lower duration of the disease.

In patients with vitiligo anti-TPO antibody titers were ranging from 5.1 to 294.4 IU/mL. In control group anti-TPO antibody titers were ranging from 4.4 to 129 IU/mL. Anti-TPO antibodies in 11 (27%) patients were higher than the normal antibody titers. In the control group, two subjects (5%) had positive anti-TPO. The frequency of anti-TPO was significantly higher in vitiligo patients than in control group. Statistically significant difference was also found in values of anti-TPO between patients with generalized and patients with localized vitiligo. There was no correlation between the duration of vitiligo and anti-TPO titer.

	Vitiligo group n (%)	Control group n (%)	P
Men, n (%)	20 (50)	14 (35)	
Women, n (%)	20 (50)	26 (65)	0.500*
Age range, years	11-60	16-65	
Age, mean years (SD)	34.675 (14.749)	39.750 (15.868)	0.1613**

Table 1. Demographic data of patients (Vitiligo group) and volunteers (Control group). *Chi-square test, **Mann-Whitney test

Mean age of onset (SD) (year)	31.26 (14.22)
Age of onset range (year)	6-57
Mean duration (SD) (month)	40.98 (41.65)
Duration Range (month)	2-144
Type of vitiligo n, (%)	
Generalized 12 (30)	
Localized 28 (70)	

Table 2. Clinical characteristics of vitiligo patients

	ANA		Anti-TPO (threshold value 34 IU/ml)	
Group	Negative n (%)	Positive n (%)	Negative n (%)	Positive n (%)
Vitiligo	33 (83)	7 (17)	29 (73)	11 (27)
Control	38 (95)	2 (5)	38 (95)	1 (3)
Total	71 (89)	9 (11)	67 (84)	14 (16)
Difference n (%)	5 (12)		9 (22)	
χ^2, P	χ^2=2.003, P=0.157		χ^2=5.878, P=0.0153	

Table 3. The frequencies of positive detectable ANA and anti-TPO

A Chi-square test for independence (with Yates Continuity Correction) indicated non- significant association between higher values of ANA and vitiligo, χ^2 (1, n=80)=2.003, P=0.157.

A Chi-square test for independence (with Yates Continuity Correction) indicated significant association between higher values of anti-TPO (values more than 34 IU/ml) and vitiligo, χ^2 (1, n=80)=5.878, P=0.0153.

4. DISCUSSION

A number of genetic and environmental factors have been implicated in the etiology of vitiligo, but the mechanism of initiation of melanocyte destruction and progression of disease is not yet clear (5). Melanocytes might be much more sensitive to toxic or immune mediated injury than other cutaneous cell types (6). How antibodies to pigment cells arise in vitiligo patients has not been elucidated. They might result from a genetic predisposition to immune dysregulation at the T or B cell level. The dermal and epidermal infiltrates consist of cytotoxic and helper T cells that are closely associated with the areas of melanocyte depletion. Circulating melanocyte specific cytotoxic T cells have been detected in high frequencies in vitiligo patients (3, 7).

Vitiligo has been reported in association with numerous autoimmune disorders. Based on suggested associations described in literature, we decided to evaluate the presence of antinuclear and thyroid peroxidase antibodies in patients and controls. The presence of antinuclear antibodies is a hallmark of many systemic autoimmune diseases. ANA are directed against various components of the nucleus, they have the ability to penetrate into the living cell (8), and there are indications that the penetration of autoantibodies occurs also *in vivo* and may lead to apoptotic cell death (9). In our study, we detected ANA in 7 (17%) of patients with vitiligo which was insignificantly higher than in the control group 2 (5%). Our results are same to the study of Zettinig *at al.* who also found that ANA were positive in 17% patients (10). The highest prevalence of ANA in vitiligo patients reported Paravar *at al.* (11), they found that ANA were positive in 33% cases. In contrary, in study that was carried out in Italy, ANA were positive in only 2.5% (12). These discrepancies may be due to variations in the sample

population. However, results of ANA testing have to be interpreted in the relevant clinical context.

Several authors reported a significantly increased prevalence of autoimmune thyroid disease in vitiligo patients; the rate of positivity of thyroid autoantibodies varied from 2.2% (13) to 50% (14). In addition, there is also a study reporting a significantly increased prevalence of vitiligo in patients with autoimmune thyroid disease compared to patients with non autoimmune thyroid disease (15, 16).

In accordance to previous studies, we also demonstrated that anti-TPO were significantly increased in vitiligo patients in comparison to healthy subjects. We detected elevated anti-TPO in 11 (27%) of patients with vitiligo. Compared with the control group, the frequency of anti-TPO antibodies was significantly higher in those with vitiligo. Our results are consistent with a clinical study performed by Sedighe and Gholamhossein (17). They analyzed antithyroid antibodies in 109 Iranian patients with vitiligo and found that anti-TPO were positive in 40 (36.7%) cases. Daneshpazhooh and colleagues measured the serum level of anti-TPO antibodies and reported significantly high levels in vitiligo patients compared to healthy controls (18). In study that was carried out in India, the anti-TPO antibodies were positive in 31.4% cases (19). Our findings showed that the frequency of anti-TPO were more significant than ANA. 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, and identification of at-risk cases for autoimmune thyroid diseases (20). Vitiligo precedes thyroid dysfunction by many years giving an opportunity to screen these high risk individuals prior to development of thyroid disease (21). The increased frequency of autoimmune diseases in patients with vitiligo suggests that all these conditions share a common etiologic factor.

5. CONCLUSION

The study revealed a significant association between vitiligo and thyroid autoimmunity and showed the tests used to detect thyroid autoantibodies to be relevant in patients with vitiligo. In contrary, ANA seems to have limited diagnostic relevance in routine clinical practice. Additional studies of a wider sample are warranted to confirm these findings and allow a detailed analysis. Vitiligo offers many benefits as a model for the study of autoimmunity, in that it can be used to identify the contributing roles of immunogenetics and endocrine factors in the initiation and propagation of autoimmune disease.

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