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ORIGINAL PAPER

Vitiligo: concomitant autoimmune and allergic diseases

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ABSTRACT

Introduction: Vitiligo is a chronic skin condition caused by progressive cutaneous hypomelanosis.
Aim: The aim of the study was to determine its epidemiology and clinical aspects. As considerable progress has been made in understanding of the pathogenesis of vitiligo and its classification as an autoimmune disease, the paper pays particular attention to coexisting autoimmune or atopic diseases.
Material and methods: The study included 55 patients attending the Diagnostic and Treatment Center of Skin Diseases in Lodz. Data were collected during outpatient dermatological consultation.
Results: The most common type of vitiligo was nonsegmental (85.5%) followed by segmental (12.7%) and unclassified (2.1%). The first skin lesions were mostly located on the hands (45.5%) and face (38.2%). Older patients with higher body mass index tended to demonstrate a higher body surface area. Of the patients, 63.6% demonstrated an autoimmune or atopic comorbidity, the most common of which were type 1 diabetes mellitus (18.2%), psoriasis (16.4%) or Hashimoto's thyroiditis (14.5%). Location on the face was associated with a significantly greater incidence of autoimmune or atopic co-morbidities.
Conclusions: A facial location may serve as a predictive factor for other autoimmune or atopic diseases in vitiligo patients. Determining clinical factors in vitiligo patients which could be associated with a higher risk of autoimmune comorbidities may allow for their early diagnosis and suitable treatment.

KEY WORDS

autoimmune diseases, comorbidities, atopic diseases, vitiligo, clinical aspects.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Vitiligo is a common skin disorder which affects 0.5–2% of the population [1, 2]. The disease is characterized by white patches of different shapes and sizes on the skin [3]. The typical predilection sites include the periorificial area of the face, extensor sides of the extremities and intertriginous areas. While the etiology of vitiligo remains unclear, it is widely regarded to have an immunological basis, and it is estimated that people with vitiligo have a 10–15% risk of developing other autoimmune diseases compared to 1–2% for the general population [4].

AIM

The aim of the study was to identify the epidemiological and clinical aspects of the disease, including location, size, type, course and concomitant comorbidities. A second aim was to identify potential factors that may affect the coexistence of autoimmune and atopic diseases, and may serve to predict a higher risk of these diseases, thus enabling early detection and treatment.

MATERIAL AND METHODS

Approval for the study was obtained from the Ethics Committee (RNN/167/23/KE). The study group comprised 55 patients; all were recruited from the Diagnostic and Treatment Center of Skin Diseases in Lodz. The participants were successively selected at random. The group included 40 (72.7%) women and 15 (27.3%) men.

Sex, age, age of onset and age of diagnosis of the disease were recorded, as well as data regarding concomitant diseases and clinical aspects: weight, height, duration of the disease, locations of first lesions of vitiligo (face, hands, chest, upper limbs, lower limbs). Disease progression (stable, nonstable) [5], character of skin lesions (nonsegmental, segmental, unclassified) [4, 6], the percentage of body surface area affected and current locations of lesions were assessed by dermatologists. Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the square of their height in meters.

STATISTICAL ANALYSIS

The following descriptive statistics were calculated: minimum and maximum values, arithmetic means; in addition, the standard deviations and medians were calculated for continuous variables, and the frequencies of occurrence of individual categories for categorical variables. The distribution of the continuous variables was determined using the Shapiro-Wilk test, and then compared using the Student's *t*-test or the Mann-Whitney test as appropriate. The categorical variables were compared using the χ^2 test or the χ^2 test with Yates' correction. Comparisons between continuous variables were assessed using Spearman's rank correlation coefficient. All analyses were performed using Statistica v.13. Differences were considered statistically significant for $p < 0.05$.

RESULTS

DEMOGRAPHICS, AGE OF ONSET

The mean age was 58.5 years among the studied women (from 24 to 88) and 46.2 years among the men (from 27 to 68). The mean age of diagnosis of vitiligo was 32.05 years (from 1 to 88), whereas the mean age of onset of the first whitewash spots was 29.93 years (from 1 to 88). Hence, the time from the appearance of the first lesions to the diagnosis of the disease was typically about 2.12 years (Table 1).

TABLE 1. Clinical characteristics of patients

Demographics	Overall ($n = 55$)
Sex:	
Female	40 (72.7%)
Male	15 (27.3%)
Mean age:	
Female	58.5 (24–88)
Male	46.2 (27–68)
Mean BMI	26.4
Mean diagnosis age [years]	32.1
Mean onset age [years]	30
Extension	21.7 (BSA%)
Location of the first lesions:	
Face	21 (38.2%)
Hands	25 (45.5%)
Trunk	10 (18.2%)
Upper limbs	12 (21.8%)
Lower limbs	16 (29.1%)
Type of vitiligo:	
Nonsegmental	47 (85.5%)
Segmental	7 (12.7%)
Unclassified	1 (2.1%)
Family history of vitiligo:	
Yes	8 (14.5%)
No	47 (85.5%)

LOCATION OF FIRST LESIONS

The hands were found to be the most common first location, i.e. in almost half of the patients (n = 25, 45.5%), followed by the skin of the face (n = 21, 38.2%). Other participants noted the lower limbs (n = 16, 29.1%), upper limbs (n = 12, 21.8%) and trunk (n = 10, 18.2%) (Table 1).

TYPE OF VITILIGO

The most common clinical types of vitiligo was nonsegmental (n = 47, 85.5%), followed by segmental (n = 7, 12.7%) and unclassified (n = 1, 1.8%) (Table 1).

FAMILY HISTORY OF VITILIGO

Eight from 55 (14.5%) patients had a family history of vitiligo (Table 1).

DISEASE PROGRESSION

In total, 42 (76.5%) patients reported stable progression of vitiligo and 13 (23.6%) reported unstable progression.

TABLE 2. Comorbid diseases

Comorbid disease	Overall frequency (N = 55) (%)
Alopecia areata	3 (5.5%)
Hashimoto's thyroiditis	8 (14.5%)
Graves' disease	5 (9.1%)
Systemic lupus erythematosus	0
Sjögren's syndrome	0
Psoriasis	9 (16.4%)
Atopic dermatitis	3 (5.5%)
Bronchial asthma	4 (7.3%)
Hay fever	5 (9.1%)
Allergic conjunctivitis	3 (5.5%)
Rheumatoid arthritis	2 (3.6%)
Type 1 diabetes mellitus	10 (18.2%)
Celiac disease	1 (1.8%)
Pernicious anemia	2 (3.6%)
Addison's disease	0
Myasthenia gravis	0
Crohn's disease	0
Colitis ulcerosa	0
Guillain-Barre syndrome	1 (1.8%)

COMORBID DISEASES

In total, 63.6% (n = 35) of the patients also had a comorbid disease. All assessed comorbidities were autoimmune or allergic diseases. The most frequent coexisting autoimmune disease was type 1 diabetes mellitus (T1DM), reported in 10 (18.2%) patients. The second most common was psoriasis, diagnosed in 9 (16.4%) patients and the third was Hashimoto's disease, reported in 8 (14.5%). The frequency of other diseases is presented in Table 2.

CORRELATIONS

BSA and the duration of the disease

A positive correlation was found between the duration of the disease and the percentage of affected skin area (BSA). This result was statistically significant (Spearman's rank correlation coefficient; $\rho = 0.36$, p value = 0.0135).

BSA and BMI

A significant positive correlation was also found between BMI and BSA: patients with a higher BMI tend to have a higher percentage of skin affected by whitewash spots (Spearman's rank correlation coefficient; $\rho = 0.28$, $p = 0.0385$).

Location of the first skin lesions and age of onset

The patients were divided into three age groups according to the age of onset of the disease: < 19 years old (n = 20), 19–44 years old (n = 21) and ≥ 45 years old (n = 14). The first skin lesions were most commonly observed on the lower limbs in the < 19 years group, on the hands and upper limbs in the 19–44 group and on the hands in the ≥ 45 group.

Location of skin lesions and BMI

The upper limbs were affected in 37.5 % (n = 9) of the patients with BMI < 25 kg/m^2, compared with 67.7% (n = 21) with BMI > 25 kg/m^2. This difference was statistically significant (χ^2 test, $p = 0.0255$); however, no other significant correlation was found between BMI and the chance of involvement of other body areas (Table 3).

Disease progression

BSA involvement was noted in 17.1% of the patients with stable vitiligo, and 26.5% of those with the unstable form (Mann-Whitney test; $p = 0.0293$). No correlations were noted between the type of vitiligo, location of skin lesions,

TABLE 3. Location of lesions and BMI

Location of lesions	BMI < 25 kg/m² ($N = 24$)	BMI ≥ 25 kg/m² ($N = 31$)	*P*-value
Face	19 (79.2%)	28 (90.3%)	> 0.05
Hands	18 (75%)	28 (90.3%)	> 0.05
Trunk	12 (50%)	18 (75%)	> 0.05
Upper limbs	9 (37.5%)	21 (67.7%)	0.0255
Lower limbs	6 (25%)	6 (25%)	> 0.05

TABLE 4. Location of the first skin lesions and comorbid diseases

Location of the first skin lesions	Comorbid autoimmune or allergic diseases			*P*-value
	Yes	No	Overall	
Face	20 (57.1%)	1 (5%)	21 (38.2%)	0.0005
Hands	7 (35%)	18 (51.4%)	25 (45.5%)	> 0.05
Trunk	5 (25%)	5 (14.3%)	10 (18.2%)	> 0.05
Upper limbs	4 (20%)	8 (22.9%)	12 (21.8%)	> 0.05
Lower limbs	5 (25%)	11 (31.4%)	16 (29.1%)	> 0.05

the age of disease onset, BMI and the progression of the disease.

The relationship between comorbid autoimmune or allergic disease and the location of the first skin lesions

Comorbid autoimmune or allergic diseases were significantly more prevalent among patients whose first manifestation of vitiligo was located on the face (Yates's χ^2 test, $p = 0.0005$). This group comprised 21 of all respondents (38.2%). Of this group, only one (5%) did not have any comorbidities (Table 4).

DISCUSSION

A diagnosis of vitiligo is based on clinical evaluation and does not require specialized additional tests. In most cases, the diagnosis is set on the basis of the clinical picture. The skin lesions are typically symmetrical, well-demarcated and non-scaly; they consist of chalky-white patches of various shapes and sizes, located on different parts of the body [7]. Depigmentation may also be observed on the mucous membranes [8, 9]. Although vitiligo does not cause any systemic symptoms, it is an esthetic problem that usually significantly reduces the quality of life [10, 11]. Vitiligo should be differentiated from other depigmentation diseases, such as chemically-induced leukoderma, infections, genetic syndromes, post-inflammatory hypopigmentation, idiopathic, malformations and neoplasms [12].

The condition progresses by the destruction of melanocytes within the membrane of the affected areas; however, the exact mechanism for the development of vitiligo spots remains unclear. A number of factors are considered in its pathogenesis, including genetic background, environmental factors and stress [13]. However, recent research indicates that immunological phenomena also play an important role in the development of the disease, as evidenced by the coexistence of vitiligo and other autoimmune diseases [14].

Although vitiligo occurs with the same frequency in both sexes [7], women are more likely to report to the doctor for help, probably for cosmetic reasons. These data are reflected in our study, in which women were 72.7% of the respondents.

Vitiligo affects both children and adults. Genetic and epidemiological studies indicate that vitiligo usually begins between the ages of 10 and 30, with the onset of the disease occurring before 20 years of age in more than 50% of cases. However, studies conducted in Japan and Taiwan indicated a later onset i.e. between 30 and 40 years of age [15, 16]. This is consistent with our present findings, where the mean age of onset of the first depigmentation spots was 29.93 years.

Literature data indicate that lesions most often appear on the face, dorsal surface of hands, nipples, axillae, umbilicus, sacrum, and anogenital regions [12]. Our present data indicate that the most common initial manifestation was the hands and face; this is in line with Speeckaert *et al.* [17].

In the present group, the most common clinical type of vitiligo was nonsegmental followed by segmental and

unclassified, similarly to the earlier published reports [18, 19].

In the present study, 63.6% of vitiligo patients also reported a comorbid autoimmune or allergic disease. Similar findings regarding the prevalence of comorbid autoimmune diseases have been noted previously; however, the prevalence varies considerably depending on the group of patients. Although the prevalence of one or several autoimmune diseases in people with vitiligo is generally estimated at 14.4–25%, some studies from Europe have found this value to be 15.4% [20], 23% [21] or 41.5% [22]; by contrast, in the general population, the prevalence appears to be less than 6% [15, 23, 24]. Thus, the risk of a patient with vitiligo developing another autoimmune disease is more than twice compared to that in the general population. This risk increases to more than three times in the case of two autoimmune diseases, and to more than four times in the case of three diseases [15].

There is clearly a close connection between the presence of these diseases and vitiligo. The most common comorbid diseases among our group of vitiligo patients were T1DM, psoriasis and Hashimoto's disease.

Epidemiological studies indicate that vitiligo is closely related to the occurrence of thyroid disorders [25, 26]: mean incidence of such disorders tends to be around 20–22% in vitiligo patients (range: 3.1% to 40%) [27–29], compared to only 3% to 9% in the general population [28]. Similarly, 23.6% of our patients reported experiencing thyroid diseases, including 14.5% with Hashimoto's thyroiditis and 9.1% with Grave's disease. In addition, Gill *et al.* [23] found the most common coexisting disease among vitiligo patients to be thyroid disease, i.e. in 12.3% of patients.

T1DM has been found to co-occur with vitiligo; this could be explained by the two conditions following similar paths involving cytotoxic T cells [30]. Previous studies have also reported a significant correlation between vitiligo and T1DM or type 2 diabetes mellitus (T2DM) [31]. A systematic review and meta-analysis by Nederstigt *et al.* [32] found that 2.4% of vitiligo patients also demonstrate T1DM. In contrast, in the present study, 18.2% of the patients reported T1DM.

The relationship between psoriasis and vitiligo remains to be clearly confirmed. Sawchuk *et al.* [33] report no such association; however both a metanalysis by Yen *et al.* [34] and a study by Dahir *et al.* [35], as our present findings do, suggest a positive correlation between the two diseases. If such a relationship is present, the coexistence of the two diseases could be supported by their similar pathomechanisms: both involve helper T-cell activation, resulting in their differentiation into Th1/Th17 lymphocytes, in vitiligo, and Th1/Th17/Th22, in psoriasis [36]. However, further investigations are needed to confirm this.

Certain conditions occur less frequently with vitiligo, but are still significant, such as systemic lupus erythematosus (SLE), dermatomyositis, scleroderma, myasthenia gravis, and atopic dermatitis [1, 15, 23, 37]. However, our present data do not confirm the results regarding SLE and myasthenia: none of our patients reported the presence of these diseases. This is to be expected as these are rare conditions and a larger study group may be needed to detect them.

Previous studies indicate a negligible chance at best of any relationship between vitiligo and the occurrence of pernicious anemia, inflammatory bowel disease, Sjögren's syndrome or celiac disease. Similarly, no examples of Crohn's disease, colitis ulcerosa or Sjögren's syndrome were found among the present group. However, Gill *et al.* [23] found the incidence of these diseases to be significantly higher in patients with vitiligo than in controls.

Numerous clinical studies have shown that an early onset of vitiligo correlated with a larger area of affected skin. In most patients, the percentage of affected skin increases with age due to it being a chronically progressive disease. Only about 30% of patients have a stable local condition, and spontaneous regression of vitiligo is very rare, being observed in only 0.6% of cases [22]. In addition, the extent of vitiligo lesions is associated with an increased risk of developing autoimmune diseases [23, 38].

This is confirmed by studies conducted by Nunes and Esser [29], which found that patients with depigmentation covering more than 25% of the skin surface had a 2.31-times higher risk of autoimmune thyroid disease. Similar relationships were observed by Gey *et al.* [39]. Interestingly, no such correlation was observed in the case of limited vitiligo.

In the present study, patients with higher BMI demonstrated significantly higher BSA. Recent studies have found vitiligo patients to be more likely to suffer from insulin resistance and lipid abnormalities due to elevated pro-inflammatory cytokine levels and reduced numbers of melanocytes [40]. This is also confirmed by Lyu *et al.* [41] and Aryanian *et al.* [42], who found that vitiligo patients have a higher chance of displaying the relevant components of metabolic syndrome, and who highlight the importance of monitoring BMI, blood glucose and blood pressure levels in patients with vitiligo. Versini *et al.* [43] indicate that patients with the highest weight and BMI have a lower response to treatment of autoimmune diseases. However, no previous studies have reported any association between higher BMI and location of vitiligo lesions on the upper limbs.

In our study group, higher BSA tended to be noted in patients with unstable vitiligo. No factors affecting stable

or unstable disease were identified. This confirms reports that the course of vitiligo changes throughout lifetime and is unpredictable [44].

The initial location of the lesions was found to vary depending on the age of the patient. Our observations are consistent with a study from India, in which childhood-onset vitiligo was connected with a significantly greater predilection for the lower limbs, and later-onset vitiligo with the upper limbs [45]. Similar findings were obtained in a retrospective observational cohort study in Europe [17].

Our results also indicate that the face was the most common initial predilection site in patients with coexisting autoimmune or atopic diseases. This is confirmed by van Geel *et al.* [20], who note a more frequent occurrence on the face in patients with autoimmune and autoinflammatory disease.

The study has some limitations regarding the groups, insofar that no control group was formed and a relatively small number of patients were included.

CONCLUSIONS

Age, BMI and the location of the lesions affect the clinical course of vitiligo. Our findings confirm a significantly important association between vitiligo and the occurrence of autoimmune or allergic diseases. The development of initial lesions on the face may be indicative of coexisting autoimmune or atopic comorbidities. As such, these patients should be carefully monitored for these diseases; however, further research is needed to confirm these observations. A greater awareness of these factors will help identify patients with the highest risk of comorbidities and allow early detection and treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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