ORIGINAL ARTICLE

Clinical profile of generalized vitiligo patients with associated autoimmune/autoinflammatory diseases

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Abstract

Background The significance of associated autoimmune/autoinflammatory diseases in generalized vitiligo patients with respect to their clinical profile has not yet been completely established.

Objective The objective of this study was to evaluate the clinical significance of associated autoimmune/autoinflammatory diseases in generalized vitiligo patients with respect to some general clinical variables, distribution pattern, disease activity and treatment response.

Methods Seven hundred generalized vitiligo patients were included in this retrospective observational cohort study.

Results Associated autoimmune/autoinflammatory diseases were present in 15.4% of the patient population and were more common in women compared with men, especially concerning thyroid disease. Only vitiligo patients with thyroid disease had clear different clinical characteristics. The percentage of total body surface area involvement was significantly ($P = 0.005$) higher in the presence of thyroid disease which was more pronounced in women compared with men. Patients with thyroid disease had a particular predisposition to acral and joint depigmentations. No clear differences in disease activity or response to therapy were observed in vitiligo patients with or without autoimmune/autoinflammatory disorders.

Conclusion The presence of associated autoimmune/autoinflammatory diseases seems to influence the clinical profile of generalized vitiligo patients. Our results support the hypothesis that in the presence of a thyroid disorder, the disease activity of vitiligo is more extensive, in particular on areas prone to friction.

Received: 13 January 2013; Accepted: 25 March 2013

Conflict of interest

The authors have no conflict of interest.

Funding sources

None.

Introduction

Vitiligo is a common acquired disfiguring pigmentation disorder, affecting approximately 1% of the world population. Multiple susceptibility genes and unknown environmental triggers are involved in the pathogenesis of this skin disorder, which is characterized by an unpredictable course with inter-individual different treatment responses. Although vitiligo is recognized to have an autoimmune basis (illustrated by the immune-mediated loss of melanocytes from affected regions, the identification of circulating antibodies targeting melanocyte antigens and the increased prevalence of autoimmune disorders), the association between vitiligo and autoimmune diseases has not yet fully been explained.[1,2] A shared underlying genetic susceptibility to other autoimmune diseases has been suggested in vitiligo patients. Recent genome-wide association analyses have identified new susceptibility loci for generalized vitiligo, which encode immune system proteins involved in biological pathways, probably influencing the development of autoimmunity.[3,4]

Non-segmental vitiligo is more often associated with a personal or family history of autoimmunity compared to segmental vitiligo. The reported autoimmune/autoinflammatory diseases in these patients are autoimmune thyroid disease, adult-onset diabetes mellitus type 1, alopecia areata, psoriasis, pernicious anaemia, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, autoimmune polyglandular syndromes and Addison's disease.[6,7] The frequencies of associated autoimmune diseases in patients with vitiligo appear to vary according to skin type or race.[5] As autoimmune thyroid disease (particularly Hashimoto thyroiditis and Graves disease) is the most common associated autoimmune disorder, routine examination of thyroid function and screening for the presence of thyroid autoantibodies, is commonly performed in patients with

vitiligo.[8,9] The analysis of antinuclear antibodies (ANA), other organ-specific autoantibodies, fasting blood glucose levels and complete blood count could be useful to detect other autoimmune phenomena.[10]

However, to our knowledge only a small number of studies have investigated the clinical significance of associated autoimmune diseases in vitiligo patients. The primary purpose of the current retrospective study was to compare the clinical characteristics of individuals with and without associated autoimmune/autoinflammatory diseases. This might be useful to assess which subjects should be screened for autoimmune disease. Based on our epidemiological clinical data, the influence of autoimmune/autoinflammatory diseases on the clinical profile, future course and treatment response of vitiligo was assessed.

Methods

Subjects

This is a retrospective, monocentre observational trial conducted at the Department of Dermatology of the Ghent University Hospital. Between 2008 and 2011, we recruited in a consecutive manner seven hundred patients of all ages with generalized vitiligo. Exclusion criteria were doubtful diagnoses and individuals with segmental, focal or mixed vitiligo (=combination of segmental and generalized vitiligo). The study was approved by the local ethics committee and was performed according to the Declaration of Helsinki. Written informed consents were obtained from all participants.

Study design

Data were taken by history using a standardized questionnaire (1), followed by a complete clinical examination (2) evaluation of clinical pictures (3).

1 The questionnaire included some general characteristics (age, gender, age of onset of vitiligo, disease activity, family history of vitiligo), personal and family history for autoimmune/autoinflammatory diseases (thyroid disease, diabetes mellitus type 1, alopecia areata, psoriasis, pernicious anaemia, rheumatoid arthritis, systemic lupus erythematosus and Addison's disease). Special attention was given to the disease activity status, which was scored on a 4 point scale, including active vitiligo lesions during the last 3 (score +3), 6 (score +2) or 12 (score +1) months, or stable lesions for at least 1 year (score 0). This score is a simplification of the Vitiligo Disease Activity (VIDA) score.[11]

2 Clinical examination of the whole body was performed with the aid of Wood's light. The therapeutic response was scored visually, comparing photographs of the treated area obtained at the previous visit (3–6 months ago) to the current status. Response to therapy was expressed in 'no response with further depigmentation', 'stabilization', 'repigmentation', and 'doubtful response'. Furthermore, presence and number of halo nevi were recorded.

3 In all patients, photographs were used to evaluate or check the distribution of lesions and to estimate the total body surface area (BSA) involved using the flat palm of the hand as 1% rule (the palm of a hand equals 1% of the total body surface). Location of vitiligo lesions was divided into 12 areas: head, face, neck, trunk, axillae, groins, genitals, arms, legs, hands and feet. Distribution and BSA were evaluated independently in a blinded setting by 1 observer.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 (SPSS Science, Chicago, IL, USA). All values are expressed as median interquartile range (IQR). Comparison of categorical and continuous variables was performed using, respectively, the Fisher's exact test and the Mann–Whitney *U*-test. If the same comparison was performed between more than two different groups, the Kruskal–Wallis test was used. For all tests, *P*-values of less than 0.05 were considered to indicate statistical significance. The chance of bias was reduced by recruiting a high number of patients in this study (n = 700). In the statistical analysis, adjustment for possible confounding factors was performed using a multivariate regression model.

Results

Patients

In total, 700 patients with generalized vitiligo were enrolled in this study, including 108 patients with associated autoimmune/autoinflammatory diseases. As expected, thyroid disease was the most frequent associated disorder followed by psoriasis, diabetes and alopecia areata (Table 1). At inclusion, the age of the study population group ranged from 2 to 77 years. In most patients (n = 477/676) (70.6%), the disease was active in the previous 12 months before inclusion. The percentage of affected BSA had a range of 0.5–95%.

Table 1 Frequency of different types of autoimmune/autoinflammatory disorders

Autoimmune/autoinflammatory disease	Number of patients (%)
No autoimmune disease	591/699 (84.5)
Thyroid disease	67/699 (9.6)
Psoriasis	16/699 (2.3)
Diabetes	15/699 (2.1)
Alopecia areata	9/699 (1.3)
Rheumatoid arthritis	4/699 (0.6)
Pernicious anaemia	3/699 (0.4)
Addison's disease	2/699 (0.3)
Multiple autoimmune diseases	7/699 (1.0)

Table 2 Patients' characteristics according to the presence of autoimmune/autoinflammatory diseases

	Total group	With associated AID	Without associated AID	*P*-value	Thyroid disease	No thyroid disease	*P*-value	Psoriasis	No psoriasis	*P*-value
Number of patients	700	108 (15.4%)	592 (84.6%)		67/699 (9.6%)	632/699 (90.4%)		16/622 (2.3%)	683/622 (97.7%)	
Male, *n* (%)	333 (47.6%)	46/333 (13.8%)	287/333 (86.2%)		18/333 (5.4%)	315/333 (94.6%)		11/333 (3.3)	322/333 (96.7)	
Female, *n* (%)	367 (52.4%)	62/367 (16.9%)	305/367 (83.1%)		49/366 (13.4%)	317/366 (86.6%)		5/366 (1.4)	361/366 (98.6)	
Age at inclusion (years), mean (median); IQR	32.7 (33.0); 20–44	40.5 (40.0); 32–49	31.4 (31.0); 19–43	$P < 0.001$	41.2 (40.0); 32–51	31.8 (32.0); 19–43	$P < 0.001$	40.8 (41.0); 32–49	32.5 (33.0); 20–44	$P = 0.024$
Duration of vitiligo at inclusion, mean (median); IQR	9.4 (6.0); 2–12	13.0 (10.0); 3–20	8.7 (5.0); 2–11	$P < 0.001$	15.5 (12.5); 4–27	8.69 (5); 2–11	$P < 0.001$	10.13 (8.5); 3–16	9.32 (6.0); 2–12	$P > 0.05$
Age at onset, mean (median); IQR	23.5 (22.8); 12–34	27.6 (26.5); 18–36	22.7 (21.0); 10–33	$P < 0.001$	25.9 (25.0); 17–35	23.2 (22.0); 11–34	$P > 0.05$	30.7 (30.0); 19–42	23.28 (22.0); 11–34	$P = 0.038$
Family history AI+, *n* (%)	419/691 (60.6)	76/107 (71.0)	343/583 (58.8)	$P = 0.018$	49/66 (74.2)	370/625 (59.2)	$P = 0.024$	11/16 (68.8)	408/674 (60.5)	$P > 0.05$
Family history vitiligo+, *n* (%)	237/690 (34.3)	43/108 (39.8)	194/582 (33.3)	$P > 0.05$	26/67 (38.8)	211/623 (33.9)	$P > 0.05$	7/16 (43.8)	230/674 (34.1)	$P > 0.05$
BSA affected with vitiligo, mean (median); IQR	5.2 (2.0); 1–4	7.91 (2.0); 1–5	4.73 (2.0); 1–4	$P > 0.05$	10.20 (3.0); 1–6	4.69 (2.0); 1–4	$P = 0.005$	8.07 (3.0); (1–10)	5.16 (2.0) (1–4)	$P > 0.05$
Presence of halo nevi (%)	207/679 (30.5)	26/106 (24.5)	181/573 (31.6)	$P > 0.05$	18/66 (27.3)	189/612 (30.9)	$P > 0.05$	2/15 (13.3)	205/663 (30.9)	$P > 0.05$
Presence of >3 halo nevi (%)	32/700 (4.6)	1/106 (0.9)	31/573 (5.4)	$P = 0.045$	0/66 (0)	32/612 (5.2)	$P > 0.05$	0/15 (0)	32/663 (4.8)	$P > 0.05$

Clinical significance of autoimmune/autoinflammatory diseases in vitiligo patients (Table 2)

Women reported more frequently to have an autoimmune/autoinflammatory disease (62/367; 16.9%) compared with men (46/333; 13.8%). This was most marked for thyroid disease, which was significantly more prevalent in women compared with men ($P < 0.0005$; 13.4% vs. 5.4% respectively). Vitiligo patients with an autoimmune/autoinflammatory disease had a higher frequency of a family member with an autoimmune/autoinflammatory disease ($P = 0.018$), which suggests a genetic autoimmune susceptibility. Nonetheless, familial vitiligo was not associated with an earlier age of onset, a difference in affected BSA or response to therapy.

The median BSA was higher in women, in comparison with men ($P = 0.001$). A difference in BSA affected with vitiligo could be observed between patients with and without associated autoimmune/autoinflammatory disease, although this was not statistically significant ($P = 0.069$). In contrast, patients with thyroid disease had a marked significant higher affected BSA ($P = 0.005$). After adjusting for age of onset and duration of disease, the results for an association between autoimmune/autoinflammatory diseases and an increased BSA remained insignificant, although in the subgroup of patients with thyroid disease, this was still the case ($P = 0.012$).

In patients with an autoimmune/autoinflammatory disease, the difference in BSA was higher between men and women compared to patients without autoimmune/autoinflammatory disease. This was mainly due to the higher prevalence of thyroid disease in women, which was besides psoriasis the only autoimmune/autoinflammatory disease associated with an increased affected BSA. In patients with thyroid disease, the difference in affected BSA between men and women was more pronounced compared with thyroid negative patients ($P = 0.005$). In a similar way, the affected BSA was significantly higher in women with associated thyroid disease compared to thyroid disease negative women ($P = 0.030$). In men, the analysis did not reach significance.

Vitiligo patients with an autoimmune/autoinflammatory disease combined with a familial history of autoimmune/autoinflammatory disease had the highest affected BSA ($P = 0.0001$). However, patients with an autoimmune/autoinflammatory disease had also a longer duration of disease due to a later age at inclusion (median: 5.5 years later), compared to patients without an autoimmune/autoinflammatory disease ($P = 0.0005$). This is probably caused by a delay in diagnosis of the autoimmune/autoinflammatory disease, which is often detected at later age, and should be taken into account when interpreting the differences in affected BSA. There was a significant earlier age of onset of vitiligo in patients without an autoimmune/autoinflammatory disease, but with a family history of autoimmune/autoinflammatory disease ($P = 0.0004$), which illustrates that a genetic predisposition may lead to an earlier development of vitiligo.

As could be expected considering the higher affected BSA in patients with an autoimmune/autoinflammatory disease, most body areas were more often affected in autoimmune/autoinflammatory disease positive patients. The most common body locations of vitiligo in autoimmune/autoinflammatory disease positive patients were the face followed by acral areas and extremities. The hands and wrists ($P = 0.0001$) were more frequently depigmented in autoimmune/autoinflammatory disease positive patients compared to autoimmune/autoinflammatory disease negative patients. This aligns with regions which are more vulnerable for Koebner's phenomenon due to friction (also termed KP2A).[12] Overall, the distribution of lesions in autoimmune/autoinflammatory disease positive patients is more often compatible with the vitiligo vulgaris form of vitiligo compared to autoimmune/autoinflammatory disease negative patients, as described in our article on the distribution of generalized vitiligo (simultaneous submitted to JEADV). The most remarkable difference in distribution pattern was found in vitiligo patients with thyroid disease (Fig. 1). A very high frequency of depigmentation of the hands was detected in both men (94.4%) ($P = 0.017$) and women (93.9%) ($P < 0.0001$) with thyroid disease, which occurred early in the disease process. The feet ($P = 0.004$) and elbows ($P < 0.0001$) were also typical predilection areas for vitiligo patients with thyroid disease (Fig. 1). This distribution pattern seems typical for subjects with thyroid disease as in other autoimmune/autoinflammatory diseases, vitiligo was much less frequently found on these areas. In fact, knees ($P = 0.0003$), elbows ($P = 0.043$) and hips ($P = 0.025$) were in the vitiligo subgroup with autoimmune/autoinflammatory disease excluding thyroid disease even less commonly observed compared to other vitiligo patients.

We found no difference in disease activity between patients with or without autoimmune/autoinflammatory disease. Overall, response to therapy seemed to be similar between patients with or without autoimmune/autoinflammatory disease. The chance of repigmentation after treatment in patients with autoimmune/autoinflammatory disease was 55.0% compared to 50.0% in patients without autoimmune/autoinflammatory disease ($P > 0.05$). In the subgroup of patients with thyroid disease, this difference was even more pronounced (61.9% vs. 49.4%) although not statistically significant. As reported earlier, the presence of >3 halo naevi was more frequently reported in vitiligo patients without autoimmune/autoinflammatory diseases ($P = 0.045$).[13] The occurrence of >3 halo naevi was not found in patients with thyroid disease or psoriasis.

Discussion

Vitiligo is well known to be associated with several autoimmune diseases. The question whether an associated autoimmune disease has an influence on the disease course or should be considered as a prognostic risk factor for a more active or extensive vitiligo is still unclear. In this study, the clinical profile of gener-

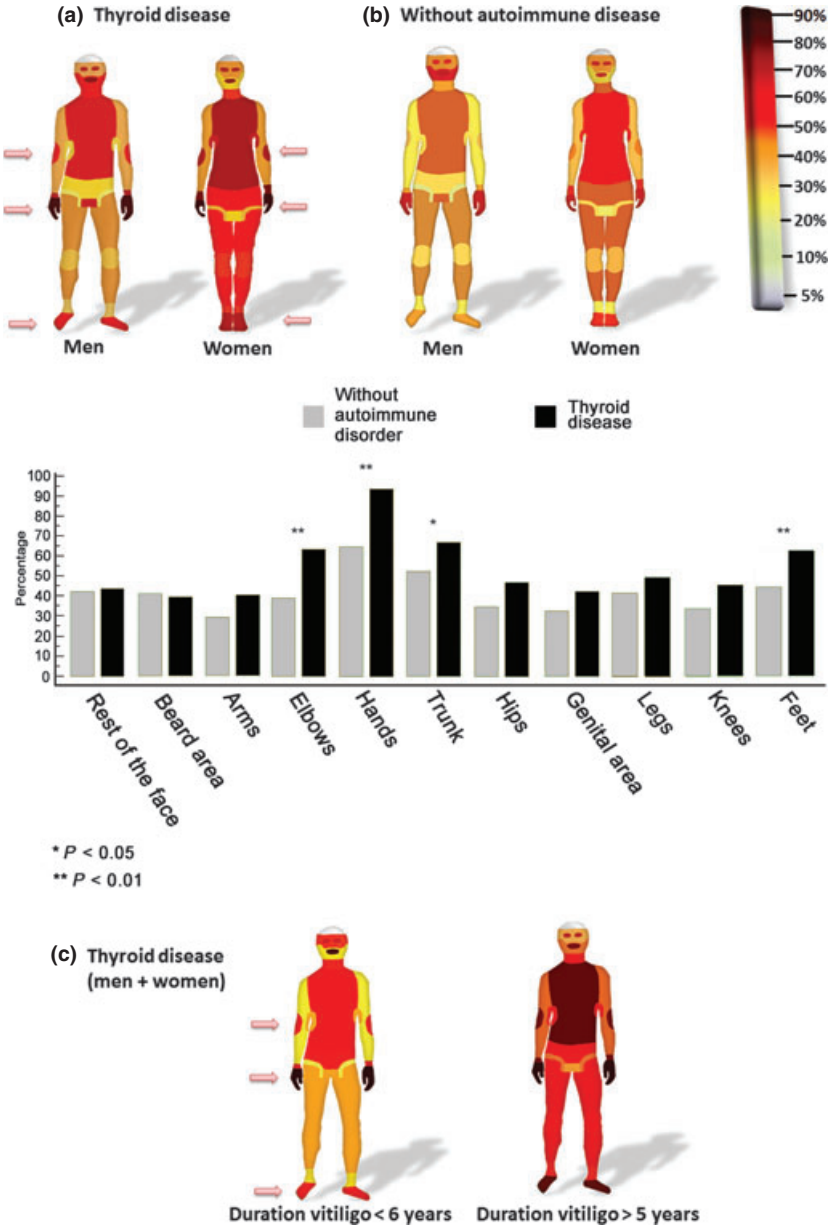

Figure 1 Distribution pattern of vitiligo: in presence of thyroid disease (a), without autoimmune disease (b) and according to duration of vitiligo in thyroid disease (men and women combined) (c). (The arrows point to the body areas with the most marked difference).

alized vitiligo patients with an autoimmune/autoinflammatory disease was compared to patients without an autoimmune/autoinflammatory disease focusing in particular on thyroid disease as being the most common type. To our knowledge, this comparison has only partially been described in the literature so far.

The affected BSA was significantly higher when thyroid disease was present. The absence of depigmentations of acral areas, especially depigmentation of the hands, is almost an exclusion criterium for the presence of thyroid disease. In this study, 19.6% of the patients with depigmentations on the hands had an associated autoimmune/autoinflammatory disease and 13.3% thyroid disease, while this was only 6.4% and 1.8% for patients without vitiligo on the hands. As 22.1% of the patients with depigmentations on hands, wrists, ankles and elbows had thyroid disease, this clinical finding may lower the threshold for screening thyroid abnormalities. These results are concordant with earlier observations, demonstrating that body locations, which are particularly prone to depigmentation due to friction (classified as KP2A), are associated with thyroid disease.[14–16] Nonetheless, other thyroid-related disorders (e.g. thyroid acropachy) tend to be also localized at acral areas of the body, although the underlying mechanisms remain obscure.[17]

Earlier it has been suggested that the link between vitiligo and autoimmune diseases may overlie internal structures

involved in this disorders. In this regard, some cases have been reported of patients with thyroid disease and depigmentations of the eyelids and neck.[18] We could not confirm this association in this study, although a slightly higher frequency of depigmentations in the neck was found in patients with thyroid disease.

Although the distribution of areas prone to koebnerization in patients with autoimmune disease could be explained by a weakened peripheral tolerance, leading to increased inflammatory responses, the reason why only thyroid disease is associated with a typical distribution pattern remains elusive. In patients with autoimmune/autoinflammatory disease excluding thyroid disease, areas of friction [elbows (men: 21.4% vs. 55.6%; women: 25.0% vs. 66.7%; $P < 0.001$), knees (men: 7.1% vs. 38.9%; women: 8.3% vs. 47.9%; $P < 0.001$), hands (men: 75.0% vs. 94.4%; women: 76.9% vs. 93.8%; $P = 0.008$), ankles (men: 17.9% vs. 38.9%; women: 8.3% vs. 44.7%; $P = 0.003$) and feet (men: 28.6% vs. 55.6%; women: 53.8% vs. 65.3%; $P = 0.010$)] were significantly less affected compared to patients with thyroid disease. Overall, thyroid disease seems the only autoimmune/autoinflammatory disorder associated with particular characteristics although a limitation of this study was the small number of patients with other types of autoimmune/autoinflammatory diseases (Table 1). Future genome-wide association studies should focus on shared autoimmune susceptibility genes, sets of specific genes and environmental triggers that might provide insights into underlying pathogenetic mechanisms.[1,19]

Vitiligo patients with a family history of an autoimmune/autoinflammatory disease had an earlier onset. This fact points to an increased susceptibility of this patient group to express clinical signs of vitiligo earlier in life. This is reinforced by the finding that vitiligo patients with an autoimmune/autoinflammatory disease also had a higher frequency of a family history of autoimmune/autoinflammatory disease. The older age of onset in vitiligo patients with a personal history of autoimmune/autoinflammatory disease could be partly explained by the presence of a subgroup of young vitiligo patients which might still develop autoimmune disease later in life. Those patients were probably false negatively characterized as having no autoimmune disease. However, future research investigating the timing of occurrence between vitiligo and other autoimmune diseases might be interesting, in particular for autoimmune/autoinflammatory diseases with skin involvement (i.e. psoriasis) to explore a direct causal or triggering relationship. A limitation of this study is that the presence of autoimmune/autoinflammatory disease was examined by a written questionnaire. Although personal autoimmune disorders are probably adequately reported by patients, determination of antibodies and thyroid function in case of thyroid disease might reveal additional information in future studies.

In conclusion, our study provides clinical evidence that autoimmune/autoinflammatory diseases, most probably only thyroid disease, might be used as a clinical parameter to predict to some extent the clinical course of vitiligo. Vitiligo patients with thyroid disease are characterized by an increased affected BSA and in particular by depigmentations on acral areas. Our study results support the hypothesis that presence of an autoimmune/autoinflammatory disease can have a prognostic value.

Acknowledgements

This study was supported by a research grant to R. Speeckaert from the Research Foundation (No. BOF10/doc/403), Ghent University and to N. van Geel from the Scientific Research Foundation-Flanders (FWO Senior Clinical Investigator).

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