

Behçet's syndrome is not associated with vitiligo

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ABSTRACT

Objective. Behçet's syndrome (BS) has many features that are different from autoimmune diseases, including a lack of association with Sjögren's syndrome. Vitiligo is frequently associated with various autoimmune disorders such as autoimmune thyroiditis, pernicious anemia and Addison's disease. Our informal observation was that vitiligo is also uncommon among BS patients. With this controlled and masked study we formally surveyed the presence of vitiligo among BS patients and suitable controls.

Methods. Patients with Behçet's syndrome, Graves' disease, and Hashimoto's thyroiditis being followed in the rheumatology and endocrinology departments of a university hospital and healthy controls were examined. Subjects with hypopigmented lesions were re-examined by a dermatologist in a masked protocol. Wood's lamp was used to confirm the diagnosis of vitiligo in suspected lesions.

Results. 253 consecutive BS patients, 34 Graves' disease patients, 32 Hashimoto's thyroiditis patients, and 439 healthy controls were surveyed. None of the BS patients had vitiligo, while 6/34 (17.6%) of Graves' disease patients, 6/32 (18.7%) of Hashimoto's thyroiditis patients, and 4/439 (0.9%) of healthy controls had vitiligo. All the subjects with vitiligo, except for one patient with associated Graves' disease, were women.

Conclusion. In contrast to two autoimmune diseases, Hashimoto's thyroiditis and Graves' disease, the frequency of vitiligo was not increased among patients with BS. This constitutes further evidence that traditional autoimmune mechanisms may not be operative in BS.

Introduction

Behçet's syndrome (BS) is a vasculitis characterized by oral and genital ulcers, papulopustular lesions, erythema nodosum, uveitis, arthritis, venous

thrombosis, arterial aneurysms, and gastrointestinal and neurological involvement. The pathogenesis of BS is not completely understood, although the role of autoimmunity has been widely discussed (1).

Vitiligo is a chronic pigmentation disorder characterized by white patches, which usually increase in size with time due to the substantial loss of functioning melanocytes. The association of vitiligo with various autoimmune disorders has been widely recognized and autoimmunity is thought to play a role in its pathogenesis (2). The frequency of autoimmune thyroid disease is increased among vitiligo patients and their first-degree relatives (3, 4), and the frequency of vitiligo is higher among patients with Hashimoto's thyroiditis and Graves' disease (5).

The aim of this study was to survey the frequency of vitiligo in patients with BS and to compare this with its occurrence in healthy controls and in patients with autoimmune thyroiditis, studied as disease controls.

Patients and methods

Consecutive BS patients who were followed in the outpatient clinic of the BS Research Center of Cerrahpasa Medical School, Istanbul University, Hashimoto's thyroiditis and Graves' disease patients followed in the endocrinology department of the same university hospital, and healthy controls were enrolled in this study. All the BS patients fulfilled the international study group criteria (6). Hashimoto's thyroiditis and Graves' disease were diagnosed based on clinical findings, thyroid function and the presence of thyroid antibodies. The subjects were thoroughly examined for hypopigmented lesions and, if any were found, they were referred to a dermatologist who was blinded to the diagnoses. He decided whether these lesions were vitiligo or not, with the help of Wood's lamp to confirm the diagnosis in suspected cases.

Competing interests: none declared.

Table I. Demographic features of the patients in each group and those with vitiligo.

	Behçet's syndrome	Hashimoto's thyroiditis	Graves' disease	Healthy controls
N	253	32	34	439
M/F	158/95	2/30	10/24	166/272
Age	36.7±9.9	46.7±10.8	38.8±11	42.4±17.7
Patients with vitiligo				
N	0	6 (18.7%)	6 (17.6%)	4 (0.9%)
M/F		0/6	1/5	0/4
Age		49.3±4.8	44±7.5	42.7±13.4

The number of patients with vitiligo in each group was compared using the Kruskal-Wallis test. Due to the high proportion of female patients among those with Hashimoto's thyroiditis and Graves' disease and those diagnosed as vitiligo, the data was also separately analyzed for the female patients.

Results

253 consecutive BS patients (158 males, 95 females, mean age 36.7±9.9 years), 34 Graves' disease patients (10 males, 24 females, mean age 38.8±11 years), 32 Hashimoto's thyroiditis patients (2 males, 30 females, mean age 46.7±10.8 years), and 439 healthy controls (166 males, 272 females, mean age 42.4±17.7 years) were surveyed (Table I).

None of the BS patients had vitiligo. Vitiligo was most frequent among Hashimoto's thyroiditis patients (6/32, 18.7%, $\chi^2_{3f}=90.98, p<0.001$), followed by Graves' disease patients (6/34, 17.6%, $\chi^2_{2f}=70.39, p<0.001$). The frequency of vitiligo was similar among BS patients and healthy controls (4/439, 0.9%, $\chi^2_{3f}=2.32, p=0.128$). In all cases the vitiligo was focal.

When the data for the female patients was analyzed separately, vitiligo was most frequent among female Graves' disease patients (5/24, 21%, $\chi^2_{3f}=51.28, p<0.001$) followed by Hashimoto's thyroiditis patients (6/30, 20%, $\chi^2_{2f}=40.91, p<0.001$), whereas the frequency among female BS patients (0/95) and healthy controls (4/272, 1.5%) was similar ($\chi^2_{3f}=1.41, p=0.235$).

Discussion

Our study shows that – in contrast to Hashimoto's thyroiditis and Graves' disease, which are autoimmune conditions

– the frequency of vitiligo among BS patients is not increased.

It was first suggested that vitiligo is an autoimmune disease, after the clinical observation that it is associated with autoimmune thyroid disease and pernicious anemia, followed by other autoimmune diseases (7). Among the rheumatologic autoimmune conditions, an increased frequency of vitiligo was reported in primary Sjögren's syndrome (8) and the frequency of systemic lupus erythematosus was increased among the first-degree relatives of vitiligo patients (4). Some authors have questioned the association between vitiligo and autoimmune thyroid disease due to the high incidence of the latter in the population (9). However, our study and other previous studies support this association, since 18.7% of our Hashimoto's thyroiditis patients and 17.6% of our Graves' disease patients had vitiligo compared to 0.9% of our healthy controls. Apart from the association with other autoimmune diseases, another finding that supports the thesis of autoimmunity in vitiligo is the presence of an anti-melanocyte antibody that reacts with melanocyte surface antigen in these patients (10). In a study aimed at identifying and characterizing the vitiligo antigens defined by antibodies in patients with vitiligo, BS patients were studied as controls and their sera were not different from normal sera when reacted with fibroblast, IGR3 and melanocyte cell lines (11).

Many clinical and epidemiological differences between BS and autoimmune diseases have been pointed out, such as the lack of dominance among females and a more severe course among males; the lack or paucity of serositis, glomerulonephritis, Raynaud's phenomenon,

peripheral neuropathy, autoimmune hemolytic anemia and thrombocytopenia; the lack of any association with autoimmune diseases such as Hashimoto's thyroiditis and Sjögren's syndrome among BS patients and their first-degree relatives; a distinct geographic distribution (along the ancient Silk Road, from the Mediterranean basin to Japan); and the paucity of BS among black people (1).

Another feature of BS that differs from autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE) is that it abates with time (12). The lack of HLA alleles and haplotypes associated with autoimmune diseases, and the lack of T cell hypofunction are further evidence against an autoimmune etiology in BS (1). Moreover, several recent reports have been published on the efficacy of TNF- α antagonists, which are contraindicated in and in fact are claimed to cause autoimmune diseases such as SLE and multiple sclerosis (13). Some features of BS – such as its response to classical immunosuppressives like azathioprine and cyclophosphamide, and autoantibodies such as anti-endothelial cell and anti-lymphocyte antibodies, and antibodies against α -tropomyosin, α -enolase and kinectin – are considered to be evidence for an autoimmune etiology (13). It was hypothesized that an antigen-driven immune response induced by heat shock proteins or other peptides from microorganisms, superimposed on an enhanced inflammatory state, may contribute to the pathogenesis of BS (14). Recently, it was suggested in a review that a new category should be defined and that BS should be included among the diseases that are unlikely to be classical autoantigen-derived autoimmune diseases (13).

Case reports of patients with BS and coexisting autoimmune disorders such as Sjögren's syndrome and diabetes insipidus have been published (15-17). In the largest case series suggesting such an association, Cho *et al.* reported 11 cases with various autoimmune disorders among their 473 patients with BS (18). However, as the authors point out, this might be a coincidental finding or could be due to clinical features such

as oral ulcers and uveitis shared by BS and SLE. The coexistence at least with Sjögren's syndrome seems to be coincidental since it was not detected when BS patients were formally surveyed for Sjögren's syndrome (19). The lack of an association between vitiligo and BS constitutes further evidence that traditional autoimmune mechanisms may not be operative in BS.

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