The prevalence of atopy and atopic diseases in Behçet's disease

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ABSTRACT

Objective. *The prevalence of Th-2 cell-mediated diseases, such as atopic diseases, has been noted to be low in Th-1 cell-mediated diseases. This study was undertaken to assess the prevalence of atopy and atopic diseases in Behçet's disease (BD), a Th-1 cell-mediated disease, and to investigate the clinical association between the atopy and the development of severe manifestations in BD.*

Methods. *We examined 70 consecutive BD patients and 113 controls without BD or other inflammatory rheumatic diseases. The cumulative history of severe manifestations in BD patients was investigated during the disease course. A skin prick test was performed in all the subjects, and atopy was defined as present when the size of one or more allergen-induced wheals was equal to or larger than that caused by histamine. Atopic diseases were defined as present when there were relevant responses for atopic diseases on the questionnaires in the subjects with atopy. In addition, serum IgE levels and peripheral blood eosinophil counts were measured.*

Results. *The prevalence of atopy and atopic diseases was significantly lower in BD patients than in controls. Other atopy parameters, such as serum IgE levels and peripheral blood eosinophil counts, were also significantly lower in BD patients when compared with controls. However, atopy, serum IgE levels, and peripheral blood eosinophil counts did not differ significantly between BD patients with and without severe manifestations.*

Conclusion. *The prevalence of Th-2 cell-mediated conditions, such as atopy and atopic diseases, appeared to be lower in BD, a Th-1 cell-mediated disease. In addition, a Th-1 and Th-2 balance may not influence the development of severe manifestations in BD.*

Introduction

According to the profile of cytokine production and effector functions, T helper (Th) cells are classified into 2 functional subsets: Th-1 and Th-2 cells. Th-1 cells, which produce interleukin (IL)-2 and interferon (IFN)-γ, are associated with the effector functions of cell-mediated immunity and of delayed type hypersensitivity reaction, and they activate macrophages which result in the production of proinflammatory cytokines, such as IL-1 and tumor necrosis factor (TNF)-α. Th-2 cells secrete IL-4, which stimulates IgE production, and IL-5, which promotes the activation and differentiation of eosinophils, and they support the B cell mediated-humoral immunity. Th-1 and Th-2 cells cross-regulate the development and function of the other subset, establishing a balance between these two types of cells. A disturbance of this balance is responsible for several pathological conditions, including allergic, autoimmune, and other immune-mediated disorders (1, 2).

Although the exact etiopathogenesis of Behçet's disease (BD) remains to be elucidated, it is believed that the disease is triggered in genetically susceptible individuals by environmental factors, such as infectious agents (3). On the other hand, there have been strong evidences that Th-1 type cytokines play an important role in the immunopathogenesis of inflammation in BD (4, 5). Recently, it has been noted that the prevalence of Th-2 cell-mediated diseases, such as atopic diseases, could be low in Th-1 cell-mediated diseases, including rheumatoid arthritis (RA) and multiple sclerosis (MS) (6-8). Furthermore, RA patients with hay fever showed less severe manifestations of RA when compared with the patients without hay fever (6). However, details on the prevalence of atopy and atopic diseases in BD patients have been limited. Therefore, this study was done to assess the prevalence of atopy and atopic diseases in BD patients, and to investigate the clinical association between atopy and the development of severe manifestations in BD.

Materials and methods

Subjects

During the period from September 2002 through November 2002, this study was prospectively undertaken on 70 consecutive BD patients (25 males and 45 females) who satisfied the International Study Group criteria (9) in rheumatology clinics at 3 tertiary referral centers located in South Korea. During the same period, the control group included 113 age- and sex-matched healthy individuals (40 males and 73 females) without BD or other inflammatory rheumatic diseases, who were chosen randomly from medical personnel and persons who visited for a medical checkup at the same medical centers. All the subjects were ethnically homogenous Koreans who were unrelated each other. The mean ages of the BD patients and controls were 39.7 ± 10.0 and 36.7 ± 10.6 years, respectively. None of them was taking antihistamines or other drugs known to affect the allergen skin test: in case of corticosteroids, subjects who had taken systemic corticosteroids (more than 10 mg/day prednisolone over 7 days) in the preceding 3 months, were excluded. The study was approved by the Hospital Ethics Committee and informed consent was obtained from all the subjects.

The cumulative history of severe manifestations in BD patients was investigated. The presence of one or more of the following clinical features during the course of the disease was regarded as a severe manifestation, as described in our previous study (10): posterior uveitis or retinal vasculitis, gastrointestinal ulcerations with bleeding or perforation, major organ involvement, or major vessel involvement.

Table I. The clinical features of 70 patients with Behçet's disease.

Clinical features	Number of patients	(%)
Oral ulcerations	70	(100)
Genital ulcerations	57	(81.4)
EN-like lesions	34	(48.6)
PPL/pseudofolliculitis	54	(77.1)
Positive pathergy reaction	21	(30.0)
Peripheral arthritis	21	(30.0)
Ocular lesions	25	(35.7)
Gastrointestinal lesions	12	(17.1)
Vascular lesions	9	(12.9)
CNS lesions	4	(5.7)

EN: erythema nodosum; PPL: papulopuspular lesions; CNS: central nervous system.

Table II. The clinical characteristics of Behcet's disease patients with severe manifestations.

Clinical features	Number of patients (%) (n = 21)
Posterior uveitis or retinal vasculitis	11 (52.4)
Central nervous system lesions	4 (19.0)
Gastrointestinal ulcerations with hemorrhage or perforation	2 (9.5)
Gastrointestinal ulcerations with perforation and retinal vasculitis	1 (4.8)
Gastrointestinal ulcerations with hemorrhage and panuveitis	1 (4.8)
Renal involvement	1 (4.8)
Femoral artery aneurysm	1 (4.8)

Allergen skin test

All the BD patients and controls were prick tested with 11 aeroallergens commonly found in the Korean atmosphere, including *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria tenuis, Aspergillus fumigatus*, dog epithelia, cat epithelia, cockroach, tree pollen mixture, grass pollen mixture, mugwort pollen, and ragweed pollen (Allergopharma, Reinbek, Germany). For positive and negative controls, histamine (1.7 mg/mL) and physiologic saline (Allergopharma, Reinbek, Germany) were used, respectively. One drop of each allergen extract and of the control solutions was introduced into intact skin on the volar side of the forearm and a 26-gauge disposable needle was used for the skin prick test (SPT). The SPT and its interpretation after 15 min were performed by trained medical personnel who were unaware of the purpose of this study. If the size of one or more allergen-induced wheals was equal to or larger than that caused by histamine, it was counted as a positive response, and we defined it as atopy.

Questionnaire

The questionnaire from Phase II modules of the International Study of Asthma and Allergies in Childhood was translated into Korean with minor modification (11, 12). The questionnaire regarding three atopic diseases, such as allergic rhinitis, bronchial asthma, and atopic dermatitis, was completed by each BD patient and control subject under the supervision of physicians. The atopic diseases were defined as present when the subjects with atopy gave the appropriate responses to questions on atopic diseases in the questionnaires.

Eosinophil and total IgE measurements

Serum total IgE was measured using a particle-enhanced nephelometric immunoassay (Dade Behring Inc., West Sacramento, CA, USA). The results were expressed as International unit (IU) per mL. In addition, peripheral blood eosinophil counts (per mm^3) were done.

Statistics

The data were analyzed using the SPSS software package (SPSS Inc., Chicago, IL, USA). The statistical significance was evaluated by Fisher's exact test or t-test where indicated. A p value less than 0.05 was considered statistically significant.

Results

The positive SPT (atopy) in 9/70 BD patients (12.9%) and 41/113 healthy controls (36.3%), respectively: compared with controls, the BD patients had a significantly lower frequency of positive SPT (p = 0.001). In addition, the mean values of serum IgE levels and peripheral blood eosinophil counts were also significantly decreased in BD patients when compared with controls [mean (range), 105.8 (4.8 – 742.0) versus 193.4 (4.8 – 2790.0) IU/mL, p =

Table III. The comparison of atopy parameters between Behcet's disease patients with and without severe manifestations.

	BD with severe manifestations (n = 21)	BD without severe manifestations (n = 49)	p value
Number of positive SPT	3 (14.3%)	6 (12.2%)	1.0*
IgE level [IU/mL, mean (range)]	111.7 (4.8 - 742.0)	103.4 (4.8 - 704.0)	0.858†
Eosinophil count [mm^3, mean (range)]	93.8 (0 - 268.0)	98.0 (7.0 - 400.0)	0.836†

BD: Behçet's disease; SPT: skin prick test.
Each p value was estimated between BD patients with and without severe manifestations; *Fisher's exact test; †t-test.

0.03; 96.8 (0 – 400.0) versus 181.3 (8.0 – 716.0) per mm^3, $p < 0.001$, respectively]. On the other hand, the prevalence of atopic diseases, including allergic rhinitis, bronchial asthma, and atopic dermatitis, is described in Figure 1. As shown, atopic diseases were noted in 5 BD patients and 24 control subjects, and the difference in prevalence was significant (7.2% versus 21.4%, $p = 0.012$).

The clinical features of the BD patients are summarized in Table I. No significant associations were found between the results of SPT and clinical features, including a positive pathergy reaction (data not shown) (all $p > 0.05$). Table II lists the clinical characteristics of BD patients with severe manifestations. The atopy parameters, including the frequency of positive SPT, serum IgE levels, and eosinophil counts in peripheral blood, did not differ significantly between BD patients with and without severe manifestations (Table III).

Discussion

There is strong evidence that Th-1 cytokine-producing cells play an important role in the pathogenesis of the inflammation in BD. The frequency of Th-1 type cytokines (IL-2 and IFN-γ)-producing T cells is increased in active BD patients, as seen in flow cytometry studies of the intracytoplasmic cytokine expression of individual cell (4, 5). In addition, Th-1 type cytokines stimulate macrophages to produce proinflammatory cytokines, such as IL-1 and TNF-α. Indeed, BD patients have an increased percentage of γδ T cells in the peripheral blood, capable of producing IFN-γ and TNF-α (13). Recently, Yamashita *et al*. found that $CD45RA^+$ γδ T cells secreting extreme amounts of TNF-α were increased in BD patients, and these cells did not produce IL-4 at all, a major cytokine of Th-2 type cells to stimulate IgE production (14). In our study, the frequencies of atopy and atopic diseases, Th-2 type cell-mediated conditions, were significantly lower in BD patients than in controls. In addition, serum IgE levels and eosinophil counts in the peripheral blood, both of which are affected by Th-2 cell type cytokines, were also significantly decreased in BD patients compared with those in controls. These results indirectly support the association of the pathogenesis of BD with Th-1 type cytokines, and not with Th-2 type cytokines.

Information on atopy and atopic diseases in BD patients has been limited. Recently, it was reported that the frequency of positive SPT in 30 BD patients was lower than that in 30 healthy controls, but this difference did not reach a statistical significance (10% versus 20%, $p > 0.05$) (15). In the current study, the frequencies of positive SPT (atopy) in BD patients and in controls were 12.9% and 36.3%, respectively ($p < 0.05$). Similarly to our control group, the frequency of atopy in general populations was reported to be 35.0% in one Korean study (16), which was also based on the results of SPT.

Since a positive SPT alone could not establish the diagnosis of the atopic diseases, we diagnosed these conditions on the basis of responses to the questionnaires by the subjects with atopy. In one Th-1 cell-mediated inflammatory disease, RA, the prevalence of atopic diseases was significantly decreased when compared with control subjects (6, 7). Verhoef *et al*. described that the prevalence of hay fever in RA patients was lower than in non-RA patients (4% versus 8%) (6). In addition, the prevalence of atopic diseases in another Th-1 cell-mediated inflammatory disease, MS, was reported to be low (4%) as well (8). In the current study, atopic diseases were found in 7.2% of BD patients, showing a significantly lower prevalence compared with controls. Our results may support the hypothesis that Th-1 cell-mediated disorders protect against the development of Th-2 cell-mediated diseases.

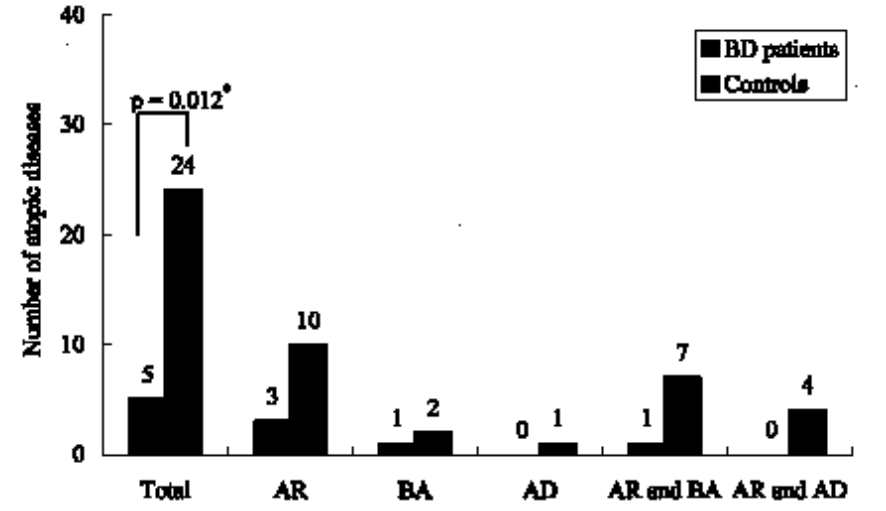

Fig. 1. Frequencies of atopic diseases in patients with Behcet's disease and controls. Those were observed in 7.2% of patients with Behcet's disease and in 21.4% of controls. BD:Behcet's disease; AR: allergic rhinitis; BA: bronchial asthma; AD: atopic dermatitis; *Fisher's exact test.

Verhoef *et al.* also reported that a RA hay fever group had a less severe and active disease than a non-RA hay fever group (6). In the current study, we investigated the cumulative history of severe manifestations in BD, because it was thought to be attributed to a long-standing disease, to determine whether the severity of BD is affected by the presence of atopy in each patient. The atopy parameters (frequency of positive SPT, serum IgE levels, eosinophil counts in peripheral blood) did not differ significantly between BD patients with and without severe manifestations. These results suggest that a Th-1 and Th-2 balance may not influence the development of severe manifestations in BD. On the other hand, although the overall frequencies of clinical features in BD patients in the current study were quite similar to other Korean studies (17),the proportion of ocular diseases (one of the severe manifestations) was relatively low. This skewed BD cohort might affect the results of this study.

To date, the studies on serum IgE levels and peripheral blood eosinophil counts have shown the conflicting results in BD patients. In one study, BD patients had higher serum IgE levels and similar peripheral blood eosinophil counts when compared with controls (18). Another study reported that IgE levels and eosinophil counts did not differ between BD patients and controls (15). However, since the former study excluded subjects with a personal or family history of atopy, it would be difficult to compare it with our results. In any case, our study, which was carried out in much larger populations than the previous studies, clearly showed significantly lower serum IgE levels and peripheral blood eosinophil counts in BD patients.

In summary, the current study revealed a lower prevalence of atopy and atopic diseases in BD patients, corroborating the hypothesis that Th-1 cell-mediated disorders protect against the development of Th-2 cell-mediated diseases.

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