Ocular Behçet's disease is less complicated with allergic disorders. A nationwide survey in Japan

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ABSTRACT

Objective. *Behçet's disease (BD) is a systemic inflammatory disorder polarised to the Th1 and Th17 immune systems. Allergic diseases are polarised to the Th2 immune system. The aim of the present study is to investigate the prevalence of allergic diseases in patients who have BD.*

Methods. *The study involved a large-scale interview survey of Japanese patients with BD at 21 institutes of ophthalmology; 353 patients (255 males and 98 females) were recruited for this study. We analysed the history of allergic diseases such as atopic dermatitis (AD), allergic rhinitis (AR), bronchial asthma (BA) and drug/food allergies (FA).*

Results. *Oral aphthous ulcers, ocular lesions, skin lesions, genital ulcers, arthritis, neurological lesions, intestinal lesions, deep vein thrombosis and epididymitis were reported in 95.8%, 98.6%, 72.5%, 44.8%, 13.9%, 6.8%, 6.2%, 3.7% and 1.4% of the patients, respectively. It was also reported that 73 patients (20.7%) had histories of allergic diseases: AD (5 cases, 1.4%), AR (36 cases, 10.2%), BA (19 cases, 5.4%) and FA (30 cases, 8.5%). This percentage was significantly lower than in a survey that Japan's Ministry of Health, Labour and Welfare conducted for healthy population (47.6%) (odds ratio = 0.29, 95% confidence interval = 0.22-0.38, $p=4.9\times10^{-22}$). Frequencies of posterior/pan-uveitis, relatively severe ocular findings, and visual prognosis were not affected by a history of allergic diseases in BD.*

Conclusion. *Patients with BD had fewer complications from allergic diseases than did the entire population of Japan.*

Introduction

Behçet's disease (BD) is a refractory, multi-systemic inflammatory disorder characterised by oral aphthous ulcers, ocular lesions, skin lesions and genital ulcers. The serum levels of cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-2, IL-8, IL-12, IL-17, IL-23 and interferon (IFN)-γ are significantly elevated in patients with BD (1). Helper T (Th) cells differentiate into Th1, Th17, Th2 or regulatory T-cells (Treg) depending on the types of cytokines. An imbalance in the Th1, Th17, Th2 and Treg cells is commonly considered to trigger the onset of various diseases (2). Th1 deviation is generated as a result of an intracellular bacterial or viral infection and is associated with cell-mediated immunity, which is responsible for organ-specific autoimmune diseases. Th17 deviation is also found in cell-mediated immunity and results from bacterial or fungal infection. Th2 deviation is generated as a result of parasitic infections or allergic diseases and is associated with humoral immunity, which is responsible for systemic autoimmune and allergic diseases. Treg suppresses the immune reaction associated with Th1, Th17 and Th2. The aim of the present study is to improve the understanding of the immune status in BD by investigating the lifetime prevalence of allergic diseases in patients who have BD.

Methods

A total of 353 Japanese patients with BD were enrolled from 21 institutes of ophthalmology that participated in this retrospective etiologic study. Medical records of the patients during 2007-2015 were reviewed. The Institutional

Review Board of Health Sciences University (No. 2015-013) and each centre approved the study protocol. BD was diagnosed according to the criteria proposed by Behçet's Disease Research Committee of Japan. Ophthalmologists carefully interviewed the patients at their clinical visits and asked them about their histories of allergic diseases, including atopic dermatitis (AD), allergic rhinitis (AR), bronchial asthma (BA), and food/drug allergies (FA) by self-enumeration. Clinical severities of the disease were evaluated by the frequencies of posterior/pan-uveitis, relatively severe ocular findings, and the best-corrected visual acuity at their final visit (visual prognosis). Informed consent was obtained from all participating individuals. The procedures used conformed to the tenets of the Declaration of Helsinki.

Japan's Ministry of Health, Labour and Welfare (MHLW) provided information about the lifetime prevalence of allergic diseases (including AD, AR, BA and FA); these diseases are estimated to affect 47.6% of the entire population, based on information from 3,321 subjects, 2,209 men (66.5%) and 1,112 women (33.5%)(3). Statistical analysis was performed using the chi-square test and Fisher's exact test (Excel, Microsoft). All *p*-values were derived from a two-sided test, and values <0.05 were considered to be statistically significant.

Results

The patients with BD included 255 males (72.2%) and 98 females (27.8%) (range 13 – 82 years old, Mean ± SD: 46.8±14.3). Oral aphthous ulcers, ocular lesions, skin lesions, genital ulcers, arthritis, neurological lesions, intestinal lesions, deep vein thrombosis and epididymitis were observed in 95.8%, 98.6%, 72.5%, 44.8%, 13.9%, 6.8%, 6.2%, 3.7% and 1.4% of the patients, respectively. Frequency of ocular symptoms was high since this survey was conducted by ophthalmology centres. AD (5 cases, 1.4%), AR (36 cases, 10.2%), BA (19 cases, 5.4%) and FA (30 cases, 8.5%) were observed in 73 patients (20.7%). The total number of patients who had histories of allergic disorders was significantly lower than in a survey (47.6%) conducted by the MHLW (odds ratio = 0.29, 95% confidence interval = 0.22-0.38, $p=4.9\times10^{-22}$, Table I).

A stratified analysis was then performed, based on the presence of oral aphthous ulcers, ocular lesions, skin lesions, genital ulcers, arthritis, neurological lesions, intestinal lesions, deep vein thrombosis and epididymitis. Posterior/pan-uveitis was seen as 87.1% in the patients with no allergic history and 86.5% in those with allergic history (not significant). Visual acuity of the final visit was 0.47 in the patients with no allergic history and 0.53 in those with a history of allergic diseases (not significant, Table I). No significant characteristics were found of an association between patients with and without allergic diseases in terms of any of the clinical manifestations.

Discussion

We conducted a nationwide survey of the prevalence of the allergic disorders in patients with BD. BD is classically considered to be a Th1- and Th17-mediated disease; however, elevated serum levels of IL-6 or IL-10 are sometimes seen, and these are associated with Th2 cytokines(4). As shown in this study, some patients with BD had histories of allergic diseases (20.7%). Immunological balance rarely stays flat throughout the duration of the disease, and the severity of BD is not the same for each patient. The conventional theory that the onset of the disease depends on the imbalance of Th1/Th17, Th2 and Treg seems applicable in BD. However, stratified analysis with or without any clinical manifestation showed no difference in terms of the prevalence of allergic diseases.

Various studies have estimated the prevalence of allergic diseases in Japan. Most of these studies were independently reported, and the prevalence of AD, AR, BA and FA is estimated to be 5.6-16.5%, 22.6-35.7%, 5.0-9.9% and 2.8-7.0%, respectively, throughout the entire Japanese population (3, 5, 6). From 1996 to 2006, these allergic diseases gradually increased in Japan, from 4.2% to 5.6% for AD ($p<0.0001$), 20.3% to 27.4% for AR ($p<0.0001$), 5.1% to 5.0% for BA ($p=0.58$) and 13.3% to 25.2% for allergic conjunctivitis ($p<0.0001$) (5). The estimated prevalence rate of Japanese cedar pollinosis also increased; it was 10.0% in the period from 1983 to 1987, but increased to 19.4% in 1996 and to 28.2% in 2006 (7). In contrast, the incidence of BD in Japan in the 1990s decreased by approximately 20% compared to the 1980s (8). BD used to be one of the three major entities of uveitis in Japan; however, it is now in sixth place as a cause of uveitis and was ranked next to acute anterior uveitis, herpetic iritis and sclerouveitis in 2010 (9). In addition, fewer ocular attacks, less immunosuppressive therapy and a tendency toward better visual acuity have recently been reported (8). These trends might be correlated with exogenous factors such as improved public health, a decrease in smoking habits and a reduction in the history of viral infection in childhood. Several studies investigated the clinical features between atopic dermatitis and Behçet's disease. They reported the lower incidence of atopic dermatitis among Behçet's patients, however no significance between their clinical manifestations and disease severity (10, 11). They were consistent with the present study. Considerable study that has been conducted into the histories of patients with BA has found that it is associated with having a dog and contracting viral infections, especially infections of the respiratory syncytial virus within the first six months after birth (12). An intervention study revealed that reduced exposure to house dust, mites and pets, less tobacco smoke in the environment, encouraging breast feeding and delaying the introduction of solids until six months of age could reduce the incidence of paediatric asthma at seven years of age by 56% (13). There has also been considerable investigation into AR, and it has been suggested that this is associated with the use of antibiotic drugs during infancy (14). In addition, it has been reported that ocular BD is influenced by unknown environmental factors that relate to specific geographical regions (15). It has been suggested that microbial antigens such

Table I. Clinical manifestations of BD and the history of allergic diseases.

		Behçet (n=353)			Japanese national survey					
		without allergy		with allergy						
		n=279	%	n=74	%	n=3,321	%	OR	95%CI	*p*
Male		202	71.4	53	71.6	2,209	66.5			
Female		77	27.8	21	28.4	1,112	33.5			
Age (mean ± SD)		47.1±14.1		45.5±15.0		18.4±0.85				NS
Oral aphtous ulcer		269	96.4	70	94.6					NS
Ocular lesion		265	95.0	73	98.6					NS
Posterior/pan-uveitis		243	87.1	64	86.5					NS
Visual acuity (mean ± SD)		0.47±0.50		0.53±0.60						NS
Skin lesion		197	70.6	59	79.7					NS
Genital ulcer		119	42.7	39	52.7					NS
Arthritis		41	14.7	8	10.8					NS
Neurological lesion		20	7.2	4	5.4					NS
Intestinal lesion		17	6.1	5	6.8					NS
Deep vein thrombosis		12	4.3	1	1.4					NS
Epididymitis		3	1.1	2	2.7					NS
Allergic disorders	total			74	21.0**	1,577	47.6	0.29	0.22-0.38	4.9×10^{-22}
	AD			5	1.4**	547	16.5	0.073	0.030-0.18	4.9×10^{-14}
	AR			37	10.5**	1186	35.7	0.2	0.14-0.29	3.3×10^{-22}
	BA			20	5.7**	329	9.9	0.52	0.32-0.83	0.0057
	FA			30	8.5	233	7			NS

AD: atopic dermatitis; AR: allergic rhinitis; BA: bronchial asthma; FA: food/drug allergy; OR: odds ratio; CI: confidence interval.
**Significant results are shown.

as *Streptococcus sanguinis*, heat shock protein (HSP) 65 and retinal S antigen are environmental factors associated with BD (1). However, these findings continue to be inconclusive.

In this type of study, there will be sources of bias that may distort the results. We identified the following possibilities:

(i) *Population bias*: we investigated the history of allergic diseases in BD patients at clinics, and in new students of a university as their health checkup. The mean ages of the 2 groups were different. The use of different study population may lead to different results, and the age gap may influence the results. However this study focused the "history" of allergic disorders. The history of allergic diseases is expected higher percentage in older (patients) than younger (healthy) groups, but is opposite according to the survey results. It is thought that the prevalence of allergic disorders may be substantially lower in Behçet's disease than healthy population. It can be also added that doctors interviewed carefully and no elderly people with beyond recall were recruited. Also, severe ocular symptoms affect mostly men in Behçet's disease. We adopted the control survey of similar male-to-female ratio with our study.

(ii) *Methodology bias*: Patients were interviewed at clinics and healthy new students were asked and answered at their clinical checkup. The different diagnostic methods may affect the results in part.

(iii) *Ascertainment bias*: No allergists participated in this study. Some people with quite mild systemic symptoms might be misidentified as no manifestations of allergy.

It is not known exactly why there was no significant difference of clinical severity and visual prognosis between allergic and non-allergic patients of BD. BD has been getting milder and the visual prognosis has been also getting better according to new effective drugs in Japan recent years. Further studies are required in other countries.

In conclusion, the prevalence of allergic diseases in patients with BD was found to be less than in the entire Japanese population. This finding could shed new light on the role of T-cell-mediated diseases and could be helpful in understanding the contribution of T-cell aberrations in the pathogenesis of BD. In addition, activating Th2 and Treg immune response may help to reduce the incidence of BD in the future.

Key messages

- The prevalence of allergic diseases in patients with Behçet's disease was investigated.
- The prevalence of allergic diseases in Behçet's disease is lower than in the Japanese population.
- The number of cases of Behçet's disease are decreasing in Japan.

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