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Original Article

Increased incidence of allergic disorders and elevated food-specific serum IgG4 levels in Japanese patients with Crohn's disease

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Abstract

An allergic response to foreign intestinal antigens such as those contained in food has been implicated as a causative factor in the development of inflammatory bowel disease (IBD). In this study, we investigated the incidence of food allergy and other allergic disorders in Japanese patients with IBD. In addition, levels of serum IgE and IgG4 antibodies specific to various food antigens were measured. Twenty-six patients with Crohn's disease (CD) and 32 patients with ulcerative colitis (UC) were studied. Two sex- and age-matched controls were selected for each patient. The incidence of food allergy (29.2%), drug allergy (28.0%), and atopic dermatitis (28.0%) in patients with CD was significantly higher than in their matched controls ($P < 0.05$); however, no significant association was observed in UC patients. Levels of serum IgE specific to food allergens were similar among the groups, but the levels of IgG4 antibody specific to soybean, were significantly higher in patients with CD than in UC patients or controls. Our observations suggest that allergic disorders or dysregulation of immune responses to certain intestinal antigens can be found in CD patients in Japan in association with their disease.

Key words: allergic disorder, food allergy, IgE, IgG4, inflammatory bowel disease.

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Introduction

Immunologic mechanisms appear to be involved in the pathogenesis of inflammatory bowel disease (IBD), and allergic responses to foreign intestinal antigens such as those contained in food and in commensal intestinal bacteria have been implicated in the etiology of this disorder, especially with respect to Crohn's disease (CD). In Japan, the number of patients with CD is increasing, and this increase coincides with a change in eating habits from our traditional diet to those of Western countries. It has been suggested that an elimination diet directed at specific foods can prolong the period of remission in CD.[1–3] Therapy using an elementary diet has been used in the treatment of CD, especially in Japan, and beneficial effects have been reported.[4,5] Thus, an unfavorable immunologic response to certain intestinal antigens may be important in the pathogenesis of CD, and the presence of an allergic disorder, especially a food allergy, may be a predisposing or susceptibility factor in the development of the disease. Although there have been many studies on the association of allergic disorders, including food allergies with IBD, results have been variable, and information on Japanese patients has been lacking.

In an attempt to find out more about the role an allergic predisposition plays in the development of IBD, we investigated the incidence of food allergy and other allergic disorders in Japanese patients with IBD. In addition, in order to more clearly define food antigen-specific allergic reactions, IgE and IgG4 antibodies specific to various food antigens were measured in sera from these patients.

METHODS

Twenty-six patients with CD (5 women and 21 men; age range, 19–55 years; mean age, 29 years) and 32 patients with ulcerative colitis (UC) (11 women and 21 men; age range, 18–68 years; mean age, 40 years) were studied. The diagnosis in each case was based on the history of clinical symptoms, characteristics of contrast radiologic examination, colonoscopic findings, and on the histologic features. Of the patients with CD, six had the disease limited to the ileum, seven had only colonic involvement, and both ileum and colon were affected in the other 13 patients. Among the UC patients, 13 were affected over the entire colon, nine had colitis confined to the left side, and the other 10 had sigmoid to rectal involvement. Two sex- and age-matched patients with orthopedic diseases, or healthy individuals without any gastrointestinal disease, metabolic disease, or other chronic illness, were selected as controls for each patient with CD or UC. In total, 116 persons were enrolled as controls. Allergic disorders in the CD and UC patients and in the control subjects were investigated by means of a questionnaire. Subjects were asked for information regarding past or present food allergies, drug allergies, atopic dermatitis, bronchial asthma, allergic rhinitis, and allergic conjunctivitis that had been diagnosed at medical facilities specializing in that particular disorder.

For the analysis of serum immunoglobulins, IgG, IgA, and IgM were measured using laser nephelometry, and IgE was measured using a radioimmunosorbent assay.[6] Serum IgE and IgG4 antibodies specific to food antigens were measured with a CAP Phadiatop radioimmunoassay (RIA) kit (Pharmacia Diagnostics, Milton Keynes, UK)[7] and enzyme-linked immunosorbent assay,[8] respectively. Five major food antigens (egg white, milk, rice, wheat, and soybean) were focused on in this study as all have been implicated as causal food antigens in several allergic disorders such as atopic dermatitis.[9]

For statistical evaluation, contingency table analysis, Student's *t*-test, and Mann–Whitney's *U*-test were used.

RESULTS

Incidence of allergic disorders

The incidence of an associated food allergy (29.2%), drug allergy (28.0%), or atopic dermatitis (28.0%) in patients with CD was significantly higher than that in their matched controls ($P < 0.05$; contingency table analysis), whereas that of bronchial asthma, allergic rhinitis, or allergic conjunctivitis was not (Fig. 1). In contrast, there was no significant association with any of these allergic disorders in UC patients. Odds ratios for the association with each allergic disorder are summarized in Table 1, and for food allergy, drug allergy, and atopic dermatitis were 3.5, 3.5 and 4.5 ($P < 0.05$; contingency table analysis), respectively. Symptoms of food allergy included urticaria, eruptions, diarrhea and irritation of the throat. Drug allergies were mainly manifested by various dermatologic disorders such as eruptions. The extent and location of the intestinal disease showed no significant correlation to the incidence of allergy in either CD or UC patients. Presumptive food allergens of patients with CD were pork, meat, bonito, shrimp, crab, buckwheat, yam,

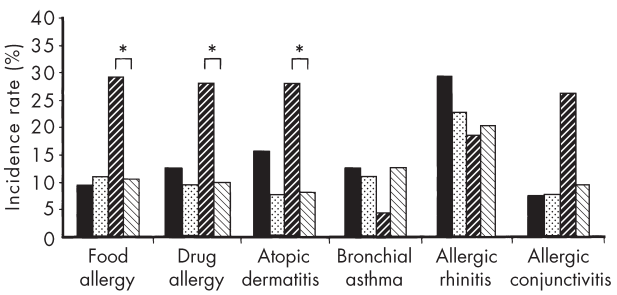

Fig. 1 Incidence of allergic disorders in patients with inflammatory bowel disease. (■), ulcerative colitis (UC); (⬚), UC control; (▨), Crohn's disease (CD); (▧), CD control. *$P < 0.05$.

Table 1 Odds ratio of allergic disorder in patients with IBD

	Ulcerative colitis			Crohn's disease		
	Odds ratio	(95% CI)	*P* value	Odds ratio	(95% CI)	*P* value
Food allergy	0.8	(0.2–3.5)	0.813	3.5	(1.0–12.7)	0.044
Drug allergy	1.4	(0.4–5.3)	0.637	3.5	(1.0–12.5)	0.045
Atopic dermatitis	2.2	(0.6–8.2)	0.238	4.5	(1.2–17.1)	0.021
Bronchial asthma	1.2	(0.3–4.3)	0.821	0.3	(0.03–2.7)	0.261
Allergic rhinitis	1.5	(0.5–4.2)	0.466	0.9	(0.2–3.2)	0.827
Allergic conjunctivitis	1.0	(0.2–5.8)	> 0.999	3.7	(0.9–15.1)	0.052

IBD, inflammatory bowel disease; CI, confidence interval.

and greasy food. Drug allergies were mostly caused by antibiotics and non-steroid anti-inflammatory drugs, all of which had been taken orally.

Serum immunoglobulins

Levels of serum IgG, IgA, and IgM were measured in 21 patients with CD and 16 patients with UC, and that of serum IgE was measured in 19 with CD and 21 with UC. Serum levels of these immunoglobulins were mostly within their normal ranges (Figs 2,3) and there were no significant differences between immunoglobulin levels in CD and UC patients. Five patients with CD and six patients with UC had serum IgE levels that were above the normal range, and all these patients had allergic disorders.

Food-specific IgE was studied in 16 patients with CD, 19 patients with UC, and in 10 healthy controls. In addition, sera from 15 patients with CD, 15 with UC, and 10 healthy controls were also analyzed for food-specific IgG4. Serum levels of IgE to the five food allergens (egg white, milk, rice, wheat and soybean) were similar among the three groups (Fig. 4). In contrast, levels of IgG4 antibody specific to the soybean antigen were significantly higher in patients with CD than in those with UC or in healthy controls (Fig. 5).

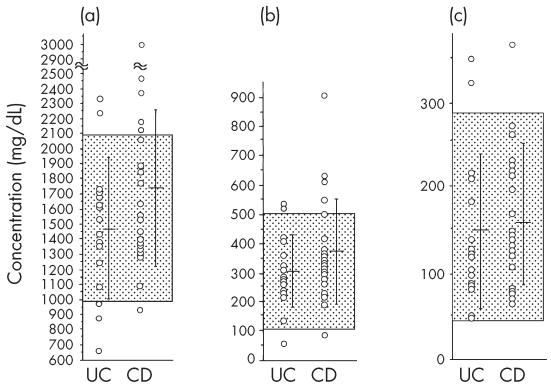

Fig. 2 Serum IgG (a), IgA (b) and IgM (c) levels in patients with inflammatory bowel disease. (⚀), normal range for each immunoglobulin. UC, ulcerative colitis (n = 16); CD, Crohn's disease (n = 21).

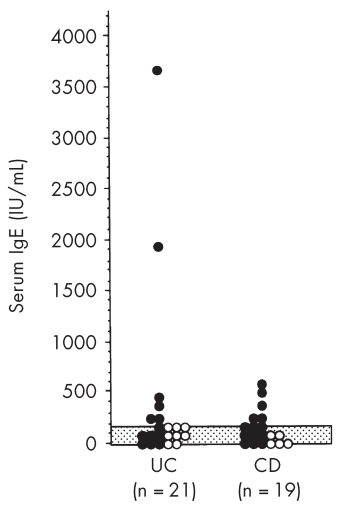

Fig. 3 Serum total immunoglobulin E levels in patients with inflammatory bowel disease, with (●) or without (○) an allergic disorder. (⚀), normal range. CD, Crohn's disease; UC, ulcerative colitis.

Discussion

Our results show that allergic disorders, particularly food allergy, drug allergy, and atopic dermatitis, are more

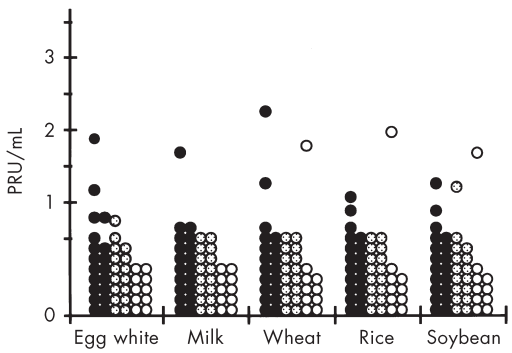

Fig. 4 Food-specific serum IgE levels in patients with inflammatory bowel disease. (●), ulcerative colitis (n = 19); (⚇), Crohn's disease (n = 16); (○), control (n = 10). PRU, Pharmacia radioallergosorbent test unit.

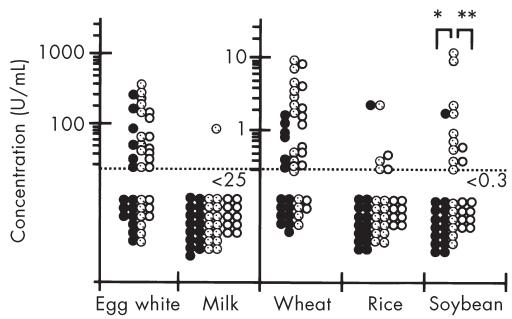

Fig. 5 Food-specific serum IgG4 levels in patients with inflammatory bowel disease. (●), ulcerative colitis (n = 15); (⚇), Crohn's disease (n = 15); (○), control (n = 10). $^{*}P < 0.01$, $^{**}P < 0.05$.

common in Japanese patients with CD than in their matched controls. In contrast, this difference was not apparent in UC patients and their controls. The fact that the incidence of these allergic disorders was similar in both matched control groups strengthens the validity of our finding. The allergic disorders observed in CD patients were mostly caused by substances taken orally (i.e. foods, antibiotics and anti-inflammatory drugs). In contrast, the incidence of other disorders, such as allergic rhinitis, which are likely due to air-borne antigens, did not show any apparent association with IBD. Since it is known that diet therapy is more crucial in the treatment of CD than in UC, our observations suggest that allergic responses against foreign intestinal antigens such as those contained in foods may be one of factors relating to the perpetuation of CD.

There have been several studies on the association of allergic disorders with IBD. Most studies[10–13] but not all[14,15] have reported an increased prevalence of eczema in patients with IBD. With respect to the incidence of other disorders, such as bronchial asthma, allergic rhinitis, and hay fever, results have been variable. With regard to food allergies, Gilat *et al*. did not find any significant difference in the incidence of allergy to milk or other foods in IBD patients compared with controls.[13] In contrast, Mee *et al*. reported that patients with IBD responded more frequently to food allergens in a prick test than did control subjects.[15]

With regard to the association of allergic disorders, including food allergy, with CD and UC, most studies did not find an apparent difference between these two diseases; however, one study described an increased incidence of eczema in CD patients but not in patients with UC.[13] In our study, a higher incidence of allergic disorders was specifically found in CD patients. We have no ready explanation for this discrepancy. In UC patients, an increased incidence of HLA-BW35 was found in a Jewish population,[16] but not in a study involving other white subjects,[17] and a decreased incidence of this antigen in Japanese cases[18] has been reported. This suggests that a racial difference in genetic background exists in UC patients. In CD patients, linkage of certain HLA haplotypes was not apparent in the white individuals[19] but was found in Japanese patients.[20,21] These findings imply that a racial difference in genetic background exists in CD patients as in UC patients, and that this may contribute to a difference in susceptibility to certain allergic diseases.

No significant difference in total serum IgE levels between CD and UC patients has been reported,[22] and the number of studies on food-specific serum antibodies in IBD patients has been limited. In a study by Jewell and Truelove, UC patients were found not to have circulating IgE-specific antibodies to milk proteins.[11] Jones *et al*. reported that total serum IgE and food-specific IgE levels to certain foodstuffs were within the normal range in UC patients.[23] In a study of monozygotic twins with IBD, twins with CD, but not those with UC, were shown to have higher antibody titers to yeast cell wall mannan than all other antibody types.[24] Elevated anti-gliadin IgA,[25] anti-bovine serum albumin IgG,[26] and IgG to baker's yeast[27] were found in CD patients but not in patients with UC. In our study, there was no apparent change in the levels of food-specific IgE in IBD patients, but we found that the serum level of IgG4 antibody specific to soybean antigen was specifically elevated in CD patients. The finding validates a further study on a larger scale.

Immunoglobulin (Ig)G4 is a subclass of IgG antibodies that has recently attracted attention as a parameter of allergic disorders; however, its definitive role as either an anaphylactic or a blocking antibody, or both, has not been fully determined.[28–32] In a study suggesting that IgG4 can act as an alternative to IgE as an anaphylactic antibody,[33] higher concentrations of casein IgG4 antibodies appeared to correlate with milk-induced eczema in adults. In our study, selective elevation of IgG4 specific to soybean was observed in CD but not in UC patients; however, no apparent relation of the food-specific IgG4 titer with the presence of symptoms of food allergy was observed. Soy sauce is a traditional soybean product and the most popular flavoring in Japan. Meals that Japanese consume daily are often flavored with soy sauce, indicating that most Japanese people are frequently exposed to this intestinal antigen. The elevation of anti-soybean IgG4 antibody could be caused by disruption of mucosal barrier due to intestinal ulcers in CD patients and be a secondary phenomenon. Nonetheless, our observations suggest that allergic disorders or dysregulation of immune responses to certain intestinal antigens can be found in CD patients in Japan in association with their disease.

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