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Helicobacter pylori infection and allergic diseases: Epidemiological study in Japanese university students

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Abstract

Background and Aim: A negative association between *Helicobacter pylori* infection and allergic diseases has not been consistent. The aim of this study was to examine the association between allergic diseases and *H. pylori* infection in Japan.

Methods: Newly enrolled university students completed health survey questionnaires regarding general health and the presence of allergic diseases. *Helicobacter pylori* status was determined by the presence of serum *H. pylori* IgG and the presence of allergic manifestations was confirmed by interview.

Results: A total of 1953 students had a routine health survey; *H. pylori* status was determined in 777 including 369 with allergic diseases and 408 controls. The reported frequency of allergic rhinoconjunctivitis, atopic dermatitis, urticaria, bronchial asthma and mixed diseases was 29.0%, 11.1%, 2.0%, 0.9% and 5.0%, respectively. *Helicobacter pylori* infection was diagnosed less frequently in the allergic group compared with controls (11.4% *vs* 17.6%, $P = 0.015$). *Helicobacter pylori* infection was less frequent in men with allergic diseases (OR 0.49, 95% CI 0.27–0.89).

Conclusion: Allergic diseases are frequent in young Japanese adults and are negatively associated with *H. pylori* infection especially in men.

Introduction

The prevalence of airway allergic diseases, such as bronchial asthma and allergic rhinitis, has increased in developed countries including Japan.[1,2] The cause(s) of this increase remains largely unknown. Proposed associations include changes in personal or maternal smoking habits;[3] exposure to food-borne and orofecal infections;[4–8] types of dwellings;[9] ownership of furry animals;[10] number of siblings, family income and education level;[11] adaptation of Western dietary habits;[12] and the presence of particulates in diesel exhaust.[13] The inverse association between family size and manifestations of allergy has been consistently found.[14–17] There is also a much-published potential link between allergy and childhood infection.[8,14,18,19] The hygiene hypothesis states that atopic sensitization to environmental allergens is related to improved hygiene which results in reduced stimulation of the immune system (e.g. the gut-associated lymphoid tissue).[20,21] Although not supported by all epidemiologic studies,[14,22] this hypothesis is supported both by studies in animals[23] and in humans, showing that the frequency of atopic disease is reduced in those who were exposed to infections (e.g. measles, tuberculosis or hepatitis A) during childhood.[6,24,25] An example is the study of Matricardi *et al.* who reported that exposure to orofecal infections (e.g. *Helicobacter pylori*, hepatitis A or *Toxoplasma gondii*) was negatively associated with allergic respiratory diseases.[4] We report the results of a survey of a large sample of university students aged 18–25 years that examined the prevalence of reported allergic diseases in relation to gender and to *H. pylori* infection.

Methods

This was an observational cross-sectional study conducted at the Health Administration Center at Wakayama University. The study was done as part of annual health check-up in the spring of 2005 and 2006. Newly enrolled university students have a routine health survey and laboratory work including the completion of an annual questionnaire consisting of 80 yes or no items regarding general health. Symptoms related to allergic diseases, such as pruritus of skin or eye, nasal discharge, cough and dyspnea, were involved in the questionnaire. An additional questionnaire covered recent or present clinical history of atopic dermatitis, allergic rhinoconjunctivitis, bronchial asthma and urticaria. After written informed consent, all students with gastrointestinal (GI) symptoms ($n = 299$) and 923 randomly selected students without GI symptoms were invited for interview to confirm the presence of allergic diseases. The allergic diseases were diagnosed based on the clinical symptoms and clinical or treatment history in medical offices and hospitals. These students were also asked for a blood sample to test *H. pylori* infection status. *Helicobacter pylori* status was determined by the presence of serum *H. pylori* IgG antibodies

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Table 1 Clinical data of the total subjects who completed the regular questionnaire and the subgroup evaluated for *Helicobacter pylori* infection

	Total† $n = 1953$			Subgroup evaluated for *H. pylori* $n = 777$		
	Allergic group $n = 709$	Non-allergic group $n = 1244$	*P*	Allergic group $n = 369$	Non-allergic group $n = 408$	*P*
Gender (M/F)	446/263	795/449	0.66§	215/191	178/193	0.22§
% of men	63.9	62.9		52.7	48.2	
Age mean (SD) year	19.5 (1.1)	19.5 (1.0)	0.95¶	19.5 (1.5)	19.4 (1.4)	0.32¶
Allergic diseases (%)						
Rhinoconjunctivitis	566 (29.0)			295 (38.0)		
Atopic dermatitis	217 (11.1)			102 (13.1)		
Urticaria	39 (2.0)			14 (1.8)		
Bronchial asthma	18 (0.9)			6 (0.7)		
Mixed	98 (5.0)			53 (6.8)		

†Total subjects who completed the regular questionnaire.
§By Mantel–Haenszel χ^2 analyses.
¶By unpaired *t*-test.

tested with an enzyme-linked immunosorbent assay (ELISA) kit using the E plate test (Eiken Kagaku, Tokyo, Japan). Exclusion criteria included failure to give informed consent and age of 25 years or older. Students were also excluded if they reported the presence of allergic diseases lacking clinical history or typical symptoms.

Statistical analyses

Values were expressed as mean ± SD. Statistical analyses for significant differences of parameters were performed using unpaired *t*-test between two groups. To assess the association between allergic diseases and *H. pylori* infection, the presence of *H. pylori* infection was evaluated as the dependent variable. Mantel–Haenszel statistics were used to assess the odds ratio (OR) and 95% confidence interval (CI). If the number of samples was less than 5, Pearson's χ^2 analyses were performed. A two-sided *P*-value of less than 0.05 was considered statistically significant. All statistical computations were performed using SPSS (version 11.0 for Windows, SPSS, Chicago, IL, USA).

Table 2 Comparisons between subjects positive and negative for *Helicobacter pylori*

	The subgroup evaluated for *H. pylori* $n = 777$		
	H. pylori-positive $n = 114$	*H. pylori*-negative $n = 663$	*P*
Gender (M/F)	58/56	335/328	1.0†
% of men	50.9	50.5	
Age mean (SD) year	19.6 (1.3)	19.4 (1.4)	0.33‡
Gastrointestinal symptoms	49 (43.0%)	250 (37.7%)	0.33
Any allergic diseases	42 (36.8%)	327 (49.3%)	0.015
Rhinoconjunctivitis	34 (29.8%)	261 (39.4%)	0.06
Atopic dermatitis	10 (8.8%)	92 (13.9%)	0.18
Urticaria	0 (0%)	14 (2.1%)	0.12
Bronchial asthma	0 (0%)	6 (0.9%)	0.60
Mixed	3 (2.6%)	50 (7.5%)	0.06

†By Mantel–Haenszel χ^2 analyses.
‡By unpaired *t*-test.

Results

The characteristics of newly enrolled university students who completed the questionnaire ($n = 1953$) are shown in Table 1. The reported frequencies were: allergic rhinoconjunctivitis (29.0%), atopic dermatitis (11.1%), urticaria (2.0%), bronchial asthma (0.9%) and more than one manifestation (5.0%). The students with GI symptoms ($n = 299$) and 923 randomly selected subjects were invited for detailed interviews.

Helicobacter pylori infection status was determined in 777 subjects and the clinical data of this subgroup are shown in Tables 1 and 2. Age, gender and the presence of GI symptoms were not significantly different between the allergic group and the non-allergic group and between the *H. pylori*-positive group and the *H. pylori*-negative group. The prevalence of *H. pylori* infection was significantly lower (11.4%) in the allergic group than in the non-allergic group (17.6%; $P = 0.015$). All students with urticaria or bronchial asthma were *H. pylori*-negative.

In the total subjects and in men, *H. pylori* infection was less frequent in the subjects with allergic diseases (total subjects, OR 0.60, 95% CI 0.40–0.90; men OR 0.49, 95% CI 0.27–0.89; Table 3). In women, however, there was no significant association between allergic disease and *H. pylori* infection. None of the men with more than one allergic disease was *H. pylori* positive; the difference in the prevalence of *H. pylori* infection was statistically significant ($P = 0.03$).

Discussion

The prevalence of airway allergic disease such as bronchial asthma and allergic rhinitis and atopy has been increasing in developed countries. We found the prevalence of self-reported allergic disorders among healthy college students was 36.3%, with rhinoconjunctivitis being the most common (29.0%). These estimates are similar to data derived from the estimated sensitization rate[26] and

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Table 3 Odds ratio of *Helicobacter pylori* infection in the subjects with allergic diseases

	n	*H. pylori*-positive (%)	Odds ratio	95% CI	*P*-value
Total	777	14.7			
Any allergic disease	369	11.4	0.60	0.40–0.90	0.01†
Rhinoconjunctivitis	295	11.5	0.66	0.43–1.01	0.06†
Atopic dermatitis	102	9.8	0.60	0.30–1.18	0.14†
Urticaria	14	0			0.24‡
Bronchial asthma	6	0			0.60‡
Mixed allergic diseases	53	5.7			0.08‡
Men	393	14.8			
Any allergic diseases	178	10.1	0.49	0.27–0.89	0.02†
Rhinoconjunctivitis	154	10.4	0.51	0.29–1.01	0.06†
Atopic dermatitis	43	4.7			0.14‡
Urticaria	6	0			0.30‡
Bronchial asthma	3	0			0.47‡
Mixed allergic diseases	26	0			0.03‡
Women	384	14.6			
Any allergic diseases	191	12.6	0.72	0.41–1.3	0.27‡
Rhinoconjunctivitis	141	12.8	0.74	0.44–1.4	0.44†
Atopic dermatitis	59	13.6	0.79	0.40–2.0	0.81†
Urticaria	8	0			0.24‡
Bronchial asthma	3	0			0.47‡
Mixed allergic diseases	27	11.1			0.60‡

†By Mantel–Haenszel chi-squared analyses.

‡By Pearson's χ^2 analyses.

consistent with estimates of the prevalence of atopy in 18-year-old Japanese adolescents in 1994–1996 which was 11% or five times greater than that of similar age groups examined 20 years previously.[27]

In 1989, Strachan proposed the 'hygiene hypothesis' that infections and living in an unhygienic environment might prime the immune system and thus 'protect' against the development of allergic diseases.[18] As a result of an increase in T helper (Th)1 cell production associated with such infections, the immune system is skewed away from Th2 cell production inducing the decrease of Th2-dominated allergic diseases.[18,28,29] Other mechanisms related to the hygiene hypothesis include the production of interleukin 10 and toll-like receptors on mononuclear cell membranes which possesses anti-allergic properties,[30,31] competition of bacterial antigens with other environmental antigens responsible for atopy[32] and components of bacterial products acting as superantigens.[33] None of these potential mechanisms have been tested formally in the context of the association between *H. pylori* and allergic diseases. Of interest, parasitic infections associated with a Th2-dominated immune response are also associated with a reduced prevalence of atopic dermatitis.[30,34,35] Matricardi *et al*. reported a negative association between atopy and evidence of prior hepatitis A virus infections, which was used as a marker of exposure to orofecal microbes.[6] They also investigated the possible association between allergic diseases and the exposure to food-borne and orofecal microbes versus airborne viruses in atopic and non-atopic male Italian military cadets and found that atopy, asthma and rhinitis were inversely related to a gradient of exposure to the microbes (*H. pylori, T. gondii*, hepatitis A) but not to the measles, mumps, rubella, chickenpox, cytomegalovirus or herpes simplex virus type 1.[4] Recent larger studies have confirmed the negative association between the prevalence of allergen-specific IgE antibodies and *H. pylori* infection.[7,8,36] Bodner *et al*., however, reported that early exposure to measles and family size were inversely related the risk of doctor-diagnosed asthma. They studied 19 cases with asthma, 150 with atopy and 190 controls and found no association between seropositivity for *H. pylori* and asthma or atopy. The prevalence of *H. pylori* infection was 31.6% in those with asthma and 51.3% in those with atopy versus 48.9% in the controls.[14] Recently, another study failed to find a consistent association of infection with hepatitis A and *H. pylori* with atopy or asthma. That study consisted of 800 samples in a community-based survey of young adults living in the UK; however, they observed an isolated negative association of sensitization to grass and evidence of infection with *H. pylori* after adjustment for age, gender, number of siblings, social class, smoking, maternal smoking and parental smoking.[37] It has been suggested that acquisition of *H. pylori* occurs in the first 5 years of life,[38] and Th1-dominated response has been detected in the gastric antrum of *H. pylori*-infected subjects.[39] Therefore *H. pylori* might be expected to have a particularly marked effect on the developing immune system and would suppress allergic immune-mediated inflammation through the Th1/Th2 paradigm, which is suppression of Th2 responses by stimulation of Th1 immunity.[7]

We evaluated 777 subjects and found that *H. pylori* infection was less frequent in the subjects with allergic diseases; however, statistical significance was not found in the subgroup analysis of only women. The influence of *H. pylori* infection on allergic disease might actually be different in women compared with men, reflecting the gender differences in other *H. pylori* associations (e.g. peptic ulcer and gastric cancer). It is also possible that the

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pathophysiology of allergic disease may differ between men and women. Evidence of a gender difference in immune responses related to inflammation has been reported in human and animal studies.[39,40] Levels of sCD14, which is involved in innate immune responses through the binding to bacterial lipopolysaccharide (LPS), and which has been implicated in the 'hygiene hypothesis' suggesting reduced allergic sensitization with bacterial stimulation, are higher in girls. The negative effects of tobacco exposure, particularly antenatal, and parental asthma are found among girls only.[40] In an animal study, female mice developed a more pronounced type of allergic airway inflammation than male mice after ovalbumin (OVA) challenge, and the numbers of eosinophils, CD4(+) T cells, B cells, and levels of IL-4, IL-13, IFN-gamma and OVA-specific IgE were higher in female than in male mice.[41] These results suggest that further studies of gender differences are needed.

In contrast, *H. pylori* infection has also been associated with extra-digestive pathologies, such as vascular diseases (coronary heart disease, primary Raynaud's phenomenon and migraine), autoimmune diseases (idiopathic thrombocytopenic purpura, Schönlein–Henoch purpura, Sjögren's syndrome and hypothyroidism) and skin disease including chronic idiopathic urticaria.[42–44] The persistent inflammatory response related to *H. pylori* infection is thought possibly to influence vascular disorders through an immune-mediated release of substances associated with vasospasm or platelet aggregation. Federman *et al*. conducted a systematic review of 10 studies investigating the link between *H. pylori* and chronic urticaria, and demonstrated that eradication of *H. pylori* was associated with remission of urticaria.[44] The association between *H. pylori* infection and chronic urticaria is still controversial and the pathogenic mechanisms have never been confirmed. Moreover, there is little evidence to support the positive association between atopic dermatitis and *H. pylori* infection.[45]

The present results support the hygiene hypothesis, and the decline of *H. pylori* infection as well as that of other orofecal and food-borne infections that stimulate gut-associated lymphoid tissue may be one of determinants of the epidemic of allergic diseases especially in men. The other epidemiologic factors relating to allergic disease, such as ownership of animals, number of siblings and family income, were not investigated in our study, and it is still unclear whether *H. pylori* per se is related to allergic disease or whether it is a surrogate marker for changes in the environment. Further large studies including those confounding factors are required to confirm the gender difference in the negative association.

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