

# Case-control study of association of eosinophilic gastrointestinal disorders with *Helicobacter pylori* infection in Japan

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(Received 1 February, 2013; Accepted 12 February, 2013; Published online 19 April, 2013)

Recent studies have suggested that decrease in *Helicobacter pylori* infection may predispose to allergic diseases. However, there are few reports of the relationships of eosinophilic gastrointestinal disorders (EGIDs), especially eosinophilic gastroenteritis (EGE), with *H. pylori* infection. We investigated the possible influence of *H. pylori* infection on EGIDs in Japanese patients. We performed a case-control study to investigate the prevalence of *H. pylori* infection in patients with EGIDs. Eighteen with eosinophilic esophagitis (EoE) and 22 with EGE were enrolled. For each patient, 3 age- and gender-matched normal controls ( $n = 120$ ) were randomly selected from a population who received a medical check-up between April 2010 and December 2011 at the Shimane Institute of Health Science. The mean ages of the EoE and EGE patients were  $50.9 \pm 17$  and  $49.2 \pm 20$  years, respectively. Males were more frequently seen in the EoE group, while there was no significant gender difference in regard to EGE. Of the patients with EoE, 22.3% were infected with *H. pylori*, as compared to 55.5% of their age- and sex-matched normal controls. The odds ratio for EoE patients to have an *H. pylori* infection was 0.22 ( $p < 0.05$ ). In addition, 22.7% of the patients with EGE and 48.5% of their matched controls were infected with *H. pylori*, with odds ratio for EGE patients to have an *H. pylori* infection shown to be 0.31 ( $p < 0.05$ ). In conclusion, the prevalence of *H. pylori* infection was significantly lower in EGE and EoE patients in Japan as compared to normal control subjects.

**Key Words:** eosinophilic esophagitis, eosinophilic gastroenteritis, *Helicobacter pylori* infection, Th2

Eosinophilic gastrointestinal disorders (EGIDs) such as eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE) have recently shown an increasing trend in Japan.<sup>(1,2)</sup> EGIDs are characterized by chronic mucosal inflammation with dense infiltration of eosinophils in esophageal squamous epithelium and gastrointestinal mucosal epithelium,<sup>(3,4)</sup> and considered to be caused by local allergic reactions, possibly to foods or airborne antigens.<sup>(5,6)</sup> The reason for the recent increase in EGID incidence has not been clarified.

*Helicobacter pylori* (*H. pylori*) infection is accepted as an important pathogenic factor in chronic gastritis, peptic ulcer diseases, gastric cancers, and mucosa-associated lymphoid tissue (MALT) lymphoma in humans.<sup>(7-9)</sup> In Japan, the rate of *H. pylori* infection has steadily decreased, partly due to improved sanitation.<sup>(10-13)</sup>

EGIDs are frequently accompanied by various types of allergic diseases such as bronchial asthma, and considered to be related to over-activation or dysregulation of Th2-mediated immune

reactions. On the other hand, for protection against bacterial infection, Th1-type immune response is believed to be important and activated by a bacterial infection. However, because of recent improvements in environmental cleanliness, the chance of bacterial infections has remarkably decreased in Japanese children. In cases of *H. pylori* infection, Th1-type immune activation occurs, though its prevalence has been rapidly decreasing.<sup>(14-18)</sup> The reduced chance of bacterial infection may result in failure to activate Th1 immune response, thus causing an imbalance between that and Th2 immune response.<sup>(19)</sup> A Th2 predominant response is prone to cause various allergic reactions. This concept is termed the hygiene hypothesis.<sup>(20)</sup> When considering this background, the decreasing rate of *H. pylori* infection may have some link to the increasing prevalence of EGIDs in Japan. There are few reports on the relationship between EGIDs (especially EGE) and *H. pylori* infection,<sup>(21,22)</sup> thus we performed a case-control study to clarify that infection rates in Japanese patients with EGIDs.

## Subjects and Methods

Eighteen patients with EoE and 22 with EGE diagnosed based on consensus diagnostic guidelines in Japan were enrolled.<sup>(23,24)</sup> For each, 3 normal age- and gender-matched control subjects ( $n = 120$ ) were randomly selected from individuals who received an annual medical check-up between April 2010 and December 2011 at the Shimane Institute of Health Science. Levels of the anti-*H. pylori* antibody were measured in serum samples obtained from all patients and controls using EIA, according to the supplier's instructions (E-PLATE 'Eiken' *H. pylori* Antibody, Eiken Chemical Co., Ltd., Tokyo, Japan).

This study was approved by the ethical committee of Shimane University Faculty of Medicine and carried out in accordance with the Declaration of Helsinki. Statistical analysis was performed using a  $\chi^2$  test. Differences at  $p < 0.05$  were considered to be statistically significant.

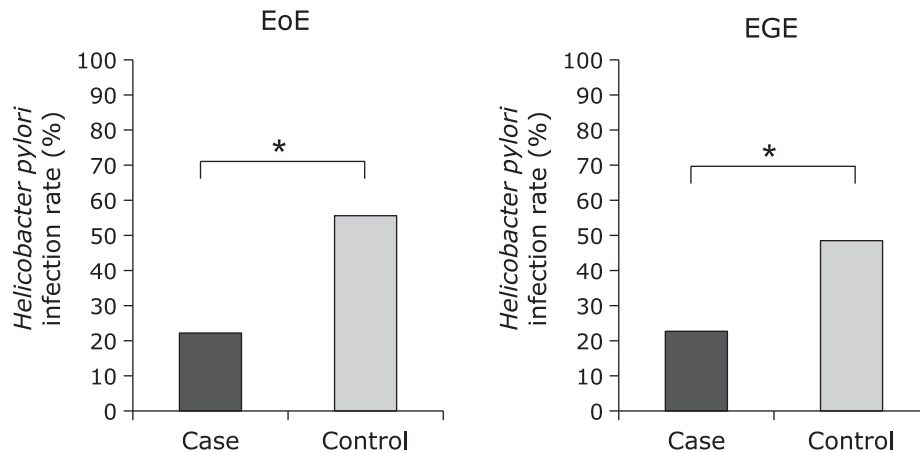
## Results

The mean ages of the EoE and EGE patients were  $50.9 \pm 17$  and  $49.2 \pm 20$  years, respectively, similar to previously reported studies in Japan.<sup>(2)</sup> The percentages of male patients were higher, especially in the EoE group (Table 1). None of the patients enrolled in this study had been treated by administration of systemic glucocorticoids. Among the EoE cases, 22.3% were

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**Table 1.** Clinical characteristics of enrolled subjects

	EoE		EGE	
	Cases	Control	Cases	Control
No. of cases	18	54	22	66
Male/Female	11/7	33/21	12/10	36/30
Mean age $\pm$ SD (years)	50.9 $\pm$ 17.4	50.5 $\pm$ 16.5	49.2 $\pm$ 20.0	49.4 $\pm$ 18.4



**Fig. 1.** The *H. pylori* infection rate was significantly lower in patients with EoE and EGE as compared to their respective age- and gender-matched controls. \*Significantly different as compared with control ( $p < 0.05$ ).

diagnosed as *H. pylori*-positive, while 55.5% of the matched controls were positive. Thus, the rate of *H. pylori* infection was significantly lower in patients with EoE as compared to the normal controls, while the odds ratio (OR) for those patients to be infected was 0.22 ( $p < 0.05$ ). As for EGE cases, 22.7% were diagnosed as *H. pylori*-positive, while 48.5% of the matched controls were positive, again showing a significantly lower rate of infection in patients with EGE as compared to the normal controls (Fig. 1). The OR for EGE patients to have an *H. pylori* infection was 0.31 ( $p < 0.05$ ).

## Discussion

EoE and EGE are allergic digestive diseases characterized by chronic inflammation along with dense mucosal infiltration of eosinophiles.<sup>(3,4)</sup> Increasing numbers of patients with EoE have been reported in Western countries,<sup>(25–28)</sup> while many cases of EGE have been reported in Japan.<sup>(1,2)</sup> It is considered that Th2-mediated allergic response and Th2-type cytokines, including IL-5, 13, 15, and eotaxins, are involved in development of these diseases.<sup>(29–33)</sup>

During an immune response, different groups of T helper (Th) cells, termed Th1 and Th2, release different patterns of cytokines. Th1 cells mediate cell-mediated immunity, as well as production of opsonizing and complement-fixing antibodies by B cells, while Th2 cells induce production of high levels of antibodies, including IgE, as well as eosinophilia.

It has been speculated that particular allergic conditions such as bronchial asthma and allergic rhinitis are increasing because of an imbalance between Th1 and Th2 type immune responses due to a modern clean lifestyle,<sup>(19)</sup> which is termed the hygiene hypothesis.<sup>(20)</sup> Th2 cytokines suppress Th1 responses, while Th1 cytokines inhibit Th2 responses and vice versa. These systems must remain in balance to maintain a healthy condition. The immune system of neonatal humans is thought to have a Th2 bias that gradually diminishes during the first 2 years of life in non-allergic individuals.<sup>(34)</sup> For development of a normal well-

balanced immune system, Th1 stimulus from the environment is necessary. Without a balanced immune system, allergic diseases are prone to occur because of the continuing Th2 bias. Many bacterial infections including mycobacteria can provide such Th1 stimulus.<sup>(35)</sup> However, because of improved sanitation and the reduced chance to have a bacterial infection during childhood, individuals have a higher chance to continue to with a skewed Th2 immune response.<sup>(36)</sup>

*H. pylori* infection is considered to be an important pathogenic factor in chronic gastritis, peptic ulcer disease, gastric cancer, and MALT lymphoma.<sup>(7–9)</sup> Due to improved sanitation and the reduced chance of infection during childhood, *H. pylori* infection is rapidly decreasing in Japan,<sup>(10–13)</sup> along with peptic ulcer diseases and gastric cancers. However, this decreased rate of *H. pylori* infection has led to increases in cases of gastric acid secretion and gastroesophageal reflux diseases.<sup>(37,38)</sup> Moreover, recent studies have suggested that a decrease in *H. pylori* infections may predispose individuals to various allergic diseases.<sup>(39)</sup> Th1-mediated response is activated in cases of infection, thus Th2 type immune response is expected to be continuously skewed in infected individuals, who are likely to become prone to Th2 type allergic responses. Common pathological conditions including exaggerated Th2 response to environmental and food allergens are considered to play important roles in the pathogenesis of EGIDs, and Dellon *et al.* recently reported that *H. pylori* infection was inversely associated with esophageal eosinophilic infiltration.<sup>(21)</sup>

In summary, we confirmed the decreased rate of *H. pylori* infection in Japanese patients with EoE as compared to the control subjects. In addition, our findings are the first to show that the *H. pylori* infection rate is lower in EGE as well as in EoE patients. Our results are limited by the relatively small sample size, and the fact that other bacterial and viral infections were not investigated. In addition, *H. pylori* infection was only determined with a serum antibody test. The specific role of the decreased rate of *H. pylori* infection should be confirmed in a larger scale prospective study.

## Acknowledgments

This study was funded in part by a Grant-in-Aid for Science Research from the Ministry of Health, Labour and Welfare of Japan (22141101).

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## Conflict of interest

No potential conflicts of interest were disclosed.

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