Retrospective Study

**Helicobacter pylori infection in patients with selective immunoglobulin E deficiency**

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Abstract

**AIM:** To investigate the prevalence and clinical characteristics of *Helicobacter pylori* (*H. pylori*)-infected dyspeptic patients with selective immunoglobulin E deficiency (IgEd).

**METHODS:** All individuals who underwent serum total immunoglobulin E (IgE) measurement at the Leumit Healthcare Services (Israel) in 2012 were identified in an electronic database search (*n* = 18487). From these, selected case group subjects were ≥ 12 years of age and had serum total IgE < 2 kIU/L (*n* = 158). The control group was selected from a random sampling of the remaining subjects ≥ 12 years of age to obtain a case-control ratio of 1:20 (*n* = 3160). Dyspeptic diseases, diagnosed no more than 5 years before serum total IgE testing, were identified and retrieved from the electronic database using specific International Classification of Diseases diagnostic codes. Results of C13-urea breath tests were used to identify subjects infected with *H. pylori*. Categorical variables between case and control subjects were analyzed using Fisher's exact tests, whereas continuous variables were analyzed using \( \chi^2 \) tests.

**RESULTS:** Dyspepsia was present in 27.2% (43/158) of case subjects and 22.7% (718/3160) of controls. Of these, significantly more case subjects (32/43, 74.4%) than controls (223/718, 31.1%) were positive for *H. pylori* (*P* < 0.01). Esophagogastroduodenoscopy was performed in 19 case and 94 control subjects, revealing that gastritis was more prevalent in IgEd case subjects than in controls (57.9% vs 29.8%, *P* < 0.05). Furthermore, a significantly greater proportion of case subjects presented with peptic duodenal ulcers (63.2% vs 15.9%, *P* < 0.01). Histopathologic examination showed marked chronic inflammation, lymphoid follicle formation and prominent germinal centers, with polymorphonuclear cell infiltration of gastric glands, that was similar in case and control biopsy tissues. Finally, IgEd case subjects that underwent esophagogastroduodenoscopy were more likely to exhibit treatment-refractory *H. pylori* infections that require second-line triple antibiotic therapy (47.4% vs 11.7%, *P* < 0.01).

**CONCLUSION:** IgEd is associated with higher rates of *H. pylori*-associated gastritis and peptic duodenal...
ulcers.

Key words: Selective IgE deficiency; Helicobacter pylori; Dyspeptic syndrome; Peptic ulcer disease; Inflammatory disease

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Core tip: A deficiency in levels of immunoglobulin E (IgEd) has been associated with chronic inflammatory diseases, immune dysregulation, oncologic diseases, and chronic infections. This retrospective case-control study evaluated the clinical characteristics of Helicobacter pylori (H. pylori)-related dyspeptic syndrome in patients with IgEd. Analyses revealed a higher prevalence of H. pylori infection in dyspeptic patients with IgEd. Furthermore, gastritis and peptic ulcer disease were more prevalent in subjects with IgEd compared with gender- and age-matched H. pylori-infected dyspeptic patients with normal or high serum IgE levels. Finally, patients with IgEd were more likely to present treatment-refractory H. pylori infections.

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INTRODUCTION

Immunoglobulin E (IgE) elicits effects that are both pathologic, as manifested in allergic disease, and beneficial, as expressed in the body’s defense against parasitic infections, particularly by helminths.[3] IgE concentrations in normal human sera are between 10 and 400 ng/mL, with a half-life of 2 to 2.5 d.[2,3] A significant decrease in these levels, to < 2 kIU/L (equivalent to 4.8 ng/mL), is defined as selective IgE deficiency (IgEd) in the case where other immunoglobulin levels are normal, or mixed IgEd if they are diminished.[4] However, this distinction is mainly a laboratory finding, as most of the affected individuals are asymptomatic.[3]

An association between IgEd and chronic inflammatory diseases of both the upper and lower respiratory tracts has been investigated[4-7], though its association to immunodeficiency remains controversial[8-11]. We recently investigated clinical and laboratory characteristics of patients with IgEd and found that adults with an undetectable serum total IgE level had immune dysregulation and autoimmunity with high prevalences of chronic infections, and autoimmune and oncologic diseases[8]. A case of persistent Helicobacter pylori (H. pylori) infection with anti-IgE biologic therapy (with omalizumab) was reported by Zandman et al.[12] who suggested that IgE may influence the inflammatory response to infection. H. pylori infection has increasingly been inversely associated with allergic diseases[13,14] and suppression of the infection improves allergic symptoms[15,16]. The primary aim of the present study was therefore to investigate the prevalence and clinical characteristics of H. pylori-infected patients with IgEd who presented with dyspeptic symptoms at the primary care setting.

MATERIALS AND METHODS

Data source

This retrospective, matched, case-control study was based on data from the Leumit Healthcare Services (Israel) Database. The database includes information on over 720000 insured people in Israel, including records of visits to clinics, laboratory test results classified by the International Classification of Diseases (ICD-9-CM), and demographic data. To maintain patient privacy, the data were extracted using unique patient identifiers. This study was approved by the committee of the Barzilai Medical Center and the Leumit Healthcare Services Institutional Review Committee.

Subjects

The database was searched for all subjects ≥ 12 years of age that had undergone serum total IgE measurements and C13-urea breath tests (C13-UBT) in 2012 for any reason. Subjects identified with serum total IgE of < 2 kIU/L were included in the case group. The control group was comprised of a random sample from the remaining subjects (serum total IgE ≥ 2 kIU/L) with a case-control ratio of 1:20. The randomization was performed using Epi Info 6 software (available from the Centers for Disease Control and Prevention; www.cdc.gov) using simple random sampling. Dyspeptic diseases were identified using specific ICD-9-CM diagnostic codes and had been diagnosed by board-certified family physicians and gastroenterologists no more than 5 years prior to serum total IgE testing. Dyspepsia was diagnosed as a syndrome consisting of pain or discomfort centered in the upper abdomen (epigastric pain), including burning, fullness, discomfort, nausea, vomiting and belching.

Criteria for exclusion from the study included: common variable immunodeficiency, chronic system corticosteroid therapy, selective IgA deficiency, ataxia telangiectasia and human immunodeficiency virus/ acquired immunodeficiency syndrome. Subjects were also excluded if they had received any form of immunosuppressive therapy during the four weeks before measurement of serum total IgE. Furthermore, subjects with alarm symptoms (weight loss, anemia, hematemesis, melena, abdominal tumor, use of non-steroidal anti-inflammatory drugs) were excluded from the study.

Ig measurements

Serum samples were analyzed for total IgE levels using
an immunometric assay on an Immulite 2000 system (Siemens, Munich, Bavaria, Germany). In all cases of serum total IgE < 2 kIU/L, other serum Igs (IgM, IgA, IgG, IgG1, IgG2, IgG3, IgG4) were routinely measured by nephelometry (BN II System; Dade Behring, Deerfield, IL, United States) to exclude humoral immunodeficiency.

Assessment of *H. pylori* infection

Trained nurses in regional laboratories performed the C13-UBT for *H. pylori* (Helicobacter Test INFAI; INFAI GmbH, Köln, Germany) and the samples were analyzed by a mass spectrometer (AP 2003; Analytical Precision, Edinburgh, United Kingdom) in the central laboratory of Leumit Health Services in Israel. Proton pump inhibitors, *H. pylori* antagonists, and antibiotics were not permitted for 15 d prior to the C13-UBT. The patients were given 75 mg urea labeled with C13 in 200 mL of orange juice, and breath samples were collected before C13 intake (T0) and 30 min later (T30). The cutoff C12/C13 at T30/T0 was 3.5 according to the manufacturer’s instructions and previous methods[17].

*H. pylori* infection was also evaluated in biopsy samples by rapid urease tests (*H. pylori* ONE kit; GI Supply, Camp Hill, PA, United States) and histological examination. Multiple gastric biopsies (two from the antrum, two from the body, and additional specimens from any lesions visible by endoscopy, if needed) were taken and stained with hematoxylin and eosin[18].

**Esophagogastroduodenoscopy**

Esophagogastroduodenoscopy (EGD) procedures were performed by experienced board-certified gastroenterologists using a video-esophago-gastro-duodenoscope (Evis Smartage Gastro GIF V70 Serial; Olympus, Shinjuku, Tokyo, Japan). Procedures were video-recorded and representative findings documented on high-resolution images.

Table 1  Clinical and laboratory characteristics of the subjects

| Characteristic                  | Cases (n = 158) | Controls (n = 3160) | P value |
|---------------------------------|-----------------|---------------------|---------|
| Female                          | 113 (%71.5)     | 2147 (%67.9)        | 0.38    |
| Age, yr                         | 44.3 ± 20.4     | 43.1 ± 22.5         | 0.51    |
| Body mass index, kg/m2          | 26.2 ± 3.5      | 26.5 ± 3.4          | 0.29    |
| Total IgE, kIU/L                | 0.3 ± 0.2       | 109.1 ± 77.6        | < 0.01  |
| WBC, n/mm3                     | 7.1 ± 3.4       | 6.8 ± 3.1           | 0.23    |
| Lymphocytes, n/mm3              | 2.4 ± 1.3       | 2.3 ± 1.1           | 0.26    |
| Eosinophils, n/mm3              | 0.31 ± 0.14     | 0.32 ± 0.11         | 0.27    |
| Basophils, n/mm3                | 0.15 ± 0.11     | 0.16 ± 0.09         | 0.18    |
| Platelets, n x 10³/mm³          | 259 ± 124       | 267 ± 129           | 0.44    |
| Dyspepsia                       | 43 (27.2)       | 718 (22.7)          | 0.47    |
| *H. pylori*-positive dyspepsia   | 32 (24.4)       | 223 (31.1)          | < 0.01  |

1Percentage reflects the proportion of dyspeptic subjects. WBC: White blood cell; IgE: Immunoglobulin E; H. pylori: Helicobacter pylori.

**H. pylori eradication regimens**

*H. pylori* eradication was comprised of a 14-d treatment with 1 g amoxicillin, 500 mg clarithromycin, and 20 mg omeprazole, bid. *H. pylori* eradication was confirmed by a second 13C-UBT eight wk following the end of the treatment. Subjects with *H. pylori* infections resistant to first-line triple therapy received a 10-d second-line therapy consisting of 40 mg pantoprazole bid along with 750 mg levofloxacin and 100 mg doxycycline, once per day.

**Statistical analyses**

Statistical analyses were performed using Statistica 6 (StatSoft Inc., Tulsa, OK, United States). Categorical variables were analyzed using a Fisher’s exact test, whereas continuous variables were analyzed using a *t* test. All values are expressed as mean ± SD. Two-tailed *P* values less than 0.05 were considered as significant.

**RESULTS**

**Demographic and laboratory characteristics of cases and controls**

A total of 18487 subjects, 4-69 years of age, were identified as having received a serum total IgE test between January 1 and December 31, 2012, primarily for allergy-related symptoms. Total serum IgE values ranged from 2 to 2000 kIU/L, and 158 case subjects ≥ 12-year-old with serum total IgE < 2 kIU/L were identified. The corresponding control group therefore consisted of 3160 subjects with serum total IgE ≥ 2 kIU/L. With the exception of serum total IgE levels, there were no differences between the cases and controls with regard to demographic and laboratory characteristics (Table 1). Although there was no difference in the percentage of subjects with dyspepsia (27.2% vs 22.7% for cases and controls, respectively), a significantly larger proportion of dyspeptic case subjects were *H. pylori*-positive (74.4% vs 31.1%, *P* < 0.01).

**EGD results**

EGD was performed on 59.4% (19/32) and 42.2% (94/223) of the *H. pylori*-positive dyspeptic cases and control subjects, respectively (Table 2). A significantly larger proportion of case subjects experienced gastritis (*P* < 0.05), which was evident particularly for multifocal atrophic gastritis. In addition, a larger proportion of case subjects presented with duodenal ulcers (63.2% vs 15.9%, *P* < 0.01). Moreover, more case subjects that underwent EGD exhibited treatment-refractory *H. pylori* infections compared to controls (47.4% vs 11.7%, *P* < 0.01). Second-line therapy successfully eradicated *H. pylori* in these subjects.

The pathologic findings from biopsied gastric tissues were similar in case and control subjects. Histopathologic analyses showed marked chronic inflammation, lymphoid follicle formation and prominent germinal centers, with
Table 2. Esophagogastrroduodenoscopy findings in Helicobacter pylori-positive dyspeptic subjects n (%).

| Characteristic                  | Cases (n = 19) | Controls (n = 94) | P value |
|--------------------------------|----------------|------------------|---------|
| Female                         | 11 (57.9)      | 49 (52.1)        | 0.81    |
| Age, yr                        | 43.9 ± 10.2    | 42.5 ± 9.7       | 0.49    |
| Gastritis                      | 11 (57.9)      | 28 (29.8)        | 0.03    |
| Antral predominant gastritis    | 7 (36.8)       | 21 (22.3)        | 0.24    |
| Body predominant gastritis      | 5 (5.3)        | 5 (5.3)          | 1.00    |
| Multifocal atrophic gastritis   | 3 (15.8)       | 2 (2.1)          | 0.03    |
| Duodenal ulcer                 | 12 (63.2)      | 15 (15.9)        | <0.01   |
| Gastric ulcer                  | 1 (5.3)        | 1 (1.1)          | 0.31    |
| Treatment-refractory H. pylori  | 9 (47.4)       | 11 (11.7)        | <0.01   |

H. pylori: Helicobacter pylori.

polymorphonuclear cell infiltration of gastric glands.

**DISCUSSION**

The results of this study show a higher prevalence of *H. pylori* infection in dyspeptic patients with IgEd. It is widely recognized that *H. pylori* infection produces strong local and systemic antibody production and cell-mediated immunity, infiltrating the gastric mucosa with inflammatory lymphocytes, macrophages, neutrophils, plasma cells, and eosinophils. Although the role of humoral immunity on bacterial colonization and the inflammatory response is poorly understood, it may provide some protection against *H. pylori* infection.

*H. pylori* directly binds to mast cells, which produce pro-inflammatory cytokines and which migrate and accumulate in the gastric mucosa. Specific antibodies are known to impair and eliminate *H. pylori* and gastric inflammation, and several lines of evidence indicate that IgE may be one such antibody. For example, IgE-positive plasma cells show significant growth in gastritis patients positive for *H. pylori*, and *H. pylori*-induced gastritis is accompanied by an increase in IgE production. These antibodies can continuously activate mast cells in mucosal tissue, and subnormal IgE levels impair the normal response of mast cells to antigens, causing Th1-related immunopathology. Specific IgE antibodies further induce receptor-specific upregulation and stabilization that is essential for establishing long-lasting mast cell memory. Therefore, failure of mast cells to function as immune guards at early stages of infection may play an important role in mediating susceptibility to *H. pylori* in patients with IgEd.

Another important finding of this study is that IgEd subjects had a higher prevalence of gastritis and peptic ulcer disease (PUD). By affecting basophils and mast cells, IgE plays an important role in T-cell activation. Whereas uncomplicated chronic gastritis is associated with a mixed Th1/Th2 response, PUD is associated with Th1 polarization of gastric cell responses in *H. pylori*-infected patients. Several studies indicate that Th1 polarization of the *H. pylori*-specific T-cell response is associated with more severe disease. The “African enigma” is a phenomenon where despite the high prevalence of *H. pylori* infection in Africa, PUD and gastric cancer are uncommon. A possible explanation is that the endemic parasitic burden causes Th2 responses to predominate, which, together with a high serum total IgE, protects *H. pylori*-infected patients from developing PUD. An increase in T-regulatory cells in infected individuals contributes to asymptomatic persistent infection, whereas subjects with inadequate T-regulatory responses develop gastroduodenal pathology. We recently found that IgEd is characterized by impaired immunologic tolerance with high rates of organ-specific and systemic autoimmune diseases. Perhaps the high rates of gastritis and PUD in the patients with IgEd and persistent *H. pylori* infection demonstrate an underlying inappropriate “tolerance” to the infection.

Some limitations of the study should be acknowledged. First, this was a retrospective study, which is vulnerable to information bias from inaccurate clinical records and missing data. Second, there are no studies of *H. pylori* bacterial virulence factors in IgEd or any experimental work to explain how IgEd facilitates the development of *H. pylori*-associated gastroduodenal disease. Third, as no *H. pylori* culturing for in vitro antibiotic sensitivity was performed following the treatment failures, we cannot determine whether IgEd is associated with infection by antibiotic-resistant *H. pylori* or with a failure to clear the *H. pylori* infection. Last, it is unclear whether IgEd patients are more susceptible to *H. pylori* infection or gastritis. Unfortunately, it was not possible to identify the rate of *H. pylori* infection in the study groups.

In summary, the results demonstrate that patients with IgEd are more prone to gastritis and PUD, as well as treatment-refractory *H. pylori* infection. However, further experimental studies are needed to assess the role of IgE in the pathogenesis of *H. pylori* infection.

**COMMENTS**

**Background**

A deficiency in levels of immunoglobulin E (IgE) has been associated with chronic inflammatory diseases, immune dysregulation, oncologic diseases, and chronic infections. A recent case involving IgE immunosuppression was associated with chronic Helicobacter pylori (*H. pylori*) infection. However, there are no published epidemiologic studies regarding the prevalence and clinical features of *H. pylori* infection in IgE deficiency (IgEd).

**Research frontiers**

Recent studies have indicated that IgEd is associated with immune-related diseases; however, the association has not been investigated in great detail, and there are no identified mechanisms for the role of IgE in immune regulation.

**Innovations and breakthroughs**

The results of this study demonstrate that subjects with IgEd have a significantly higher prevalence of *H. pylori* infection, gastritis, and peptic ulcer disease. Furthermore, treatment-refractory *H. pylori* infections were more common in IgEd subjects.

**Applications**

The results of this study suggest that IgE may play an important role in a host’s immune response to *H. pylori* infection.

**Terminology**

Dyspepsia is a syndrome consisting of pain or discomfort centered in the upper
abdomen described as a burning or fullness, which is accompanied by nausea, vomiting, and belching. *H. pylori* is a gram-negative bacterium found in the stomach that is linked to the development of gastritis, gastric ulcers, duodenal ulcers and gastric cancer.

**Peer review**

The topic of this study is very interesting, involving the evaluation of the immunologic association between a rare disease of IgEd and *H. pylori* infection. The authors found more cases of *H. pylori*-positive gastritis in patients with IgEd. The *H. pylori* eradication rate for legacy triple therapy was statistically inferior in the IgEd group compared to the control, but second-line levofloxacin-based triple therapy was equally effective for these subjects. This information is of interest for clinicians treating patients with IgEd.

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