Association of *Helicobacter pylori* IgA antibodies with the risk of peptic ulcer disease and gastric cancer

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INTRODUCTION

*Helicobacter pylori* (*H. pylori*), the causative agent of chronic gastritis[8,10], is also the most important risk factor for peptic ulcer disease and distal gastric cancer[1,4,5]. The presence of *H. pylori* antibodies signify this chronic infection and their prevalence increases with age in all populations, mainly due to the birth of cohort phenomena[6,7]. The optimal serological tests for *IgG* antibodies to *H pylori* show a sensitivity and a specificity of over 95%[9-12]. Antibodies of the *IgA* class are usually detected in combination with elevated *IgG* antibodies in approximately two-thirds of infected subjects[8,11,12,15]. They are diagnostically useful in the 2-7% of *H pylori* patients who do not have elevated *IgG* levels[17]. *IGA* antibodies have been shown to be a sensitive indicator of an increased risk for gastric cancer[14].

In this context, it may be important that subjects with CagA antibodies have more often *IgA* response, but not *IgG* response, was associated with an increased risk of CA (OR 2.41, 95%CI 1.79-3.53) and GU (OR 2.57, 95%CI 1.95-3.39) in comparison with CG patients.

RESULTS:

The prevalences of *IgG* antibodies were equally high (89-96%) in all 20-year age cohorts of the DGD groups, whereas the prevalences of *IgA* antibodies were lower and increased by age in the POPUL and NoDg groups. The prevalences of *IgA* antibodies were also higher in the DGD groups; among them CA (84-89%) and GU groups (78-91%) showed significantly higher prevalences than DU (68-77%) and CG patients (59-74%) (OR 2.49, 95%CI 1.86-3.34 between the GU and DU groups). In the CA, GU, and DU groups, the *IgA* prevalences showed only minor variation according to age, while they increased by age in the CG, POPUL, and NoDg groups (P≤0.0001). The *IgA* response, but not the *IgG* response, was associated with an increased risk of peptic ulcer disease and gastric cancer.

CONCLUSION: An *IgA* antibody response during *H pylori* infection is significantly more common in CA and GU patients as compared with CG patients.
in samples collected from the Finnish population.

MATERIALS AND METHODS

Study subjects

Serum samples for this study were obtained from 1986 to 2000 from the following patient groups: 3 252 patients with defined gastric diseases (DGD), including 482 patients with an endoscopically confirmed gastric ulcer (GU) (mean age 60.79 years, SD±12.59 years), 882 patients with an endoscopically confirmed duodenal ulcer (DU) (mean age 53.80 years, SD±15.95 years) and 363 subjects with subsequent gastric cancer (CA) (mean age 50.58 years, SD±15.95 years) and 363 subjects with histologically verified chronic gastritis (CG) (mean age 50.58 years, SD±15.95 years) and 363 subjects with subsequent gastric cancer (CA) (mean age 50.58 years, SD±15.95 years). Sera from GU, DU, and CG patients were collected on the day of the endoscopy, those from CA patients between 2 wk to 24 years before the diagnosis of cancer was made (reported in part earlier[8,10]). In the GU, DU, and CG groups, patients who had prior successful eradication therapy were excluded from the study. In addition, serum samples were obtained from 4 854 subjects participating in a population study in Vammala, Finland (POPUL) (mean age 41.73 years, SD±20.60 years), reported in part earlier[9] and from 19 145 patients whose sera were sent by general practitioners, Municipal Health Centers or Hospitals to our diagnostic laboratory for H pylori antibody tests without any information on possible gastric disorders (NoDg) (mean age 51.47 years, SD±16.97 years).

Ethics

The study was approved by the Ethics Committee for Epidemiology and Public Health of the Helsinki and Uusimaa Hospital district.

Laboratory assessment

H pylori IgG and IgA antibody titers were determined by in-house enzyme immunoassay[8,10]. The antigen used was an acid glycine extract from H pylori strain NCTC 11637. During the study period, the sensitivity and specificity of the IgG test were 95-99% and 93-97%, respectively, and those of the IgA test were 64-67% and 92-98%, respectively, as determined in patients in whom the presence of H pylori infection had been verified by culture and histology of gastric biopsies[8,10].

Statistical analysis

The trend in changes in the prevalences of IgG and IgA antibodies by age was studied using the linear trend test. The comparisons of prevalences of IgA and IgG antibodies between the groups were analyzed using the logistic regression model adjusting for age based on 1-year age cohorts. For an overview, the prevalences were determined for 20-year age-adjusted cohorts (15-34, 35-54, 55-74, and 75-94 years), each including at least 50 subjects. The association of IgA and IgG responses with the risk of serious complications (CA, GU, and DU) was analyzed using a logistic regression model by comparing the number of subjects in each antibody response and complication category to that in CG patients, who are regarded to present the basic disease caused by H pylori. Statistical analyses were carried out using the SPSS 12.0 software package (SPSS Inc., Chicago, IL, USA). P<0.05 was considered statistically significant.

RESULT

Of the 27 251 subjects, 13 939 (51.2%) were positive for H pylori antibodies. Of the antibody-positive subjects, 61.8% were positive for both IgG and IgA antibodies, 34.9% for IgG antibodies only and 3.3% for IgA antibodies only.

IgG antibody prevalences

Among the subjects in the DGD groups, 88.6-95.7% had H pylori antibodies of the IgG class in all 20-year age cohorts (Figure 1). In contrast, among the subjects representing the POPUL and NoDg groups, significantly lower seroprevalences were observed (OR 19.73, 95%CI 16.15-24.10 and OR 14.11, 95%CI 12.28-16.21, respectively) (Figure 1). Furthermore, the prevalence was seen to increase by age from 12% in the youngest cohort to 63% in the 55-74-year-old cohort in the POPUL group (P<0.0001; trend test), and from 27% to 62%, respectively, in the NoDg patients (P<0.0001; trend test). The prevalence of IgG antibodies was significantly higher in the NoDg patients than in the POPUL group (OR 2.18, 95%CI 2.00-2.36) (Figure 1).

Within the DGD group, the prevalences did not differ between the GU, DU, CG, and CA groups, nor did they show any significant variation by age (trend test).

IgA antibody prevalences

The prevalence of IgA antibodies group in all age cohorts was significantly higher in the DGD group than in the POPUL (OR 9.61; 95%CI 8.20-11.26) and NoDg groups (OR 5.00; 95%CI 4.59-5.44) (Figure 2). Within the DGD group, the highest prevalences were found in the GU and CA groups in all 20-year cohorts (77.7-90.7% and 84.3-88.6%, respectively) (Figure 2) without a significant difference between these two groups (OR 1.09, 95%CI...
Association of IgG and IgA responses with the risk of CA, GU or DU in comparison to CG

| Subjects | IgA | IgG |
|----------|-----|-----|
|        | OR  | 95%CI | OR  | 95%CI |
| CG      | 1   | 1    | 1    | 1    |
| CA      | 2.41 | 1.79-3.53 | 1.28 | 0.81-2.02 |
| GU      | 2.57 | 1.95-3.39 | 0.69 | 0.46-1.03 |
| DU      | 1.13 | 0.95-1.35 | 0.72 | 0.55-0.99 |

0.75-1.58). Although the GU patients showed a small decrease of IgA-positive subjects by increasing age (P = 0.016; trend test), the prevalence was markedly higher than in DU (68.4-77.4%, OR 2.49; 95%CI 1.86-3.34) and CG patients (58.7-74.2%, OR 2.57, 95%CI 1.95-3.39). In the DU patients, the IgA prevalence showed no significant trend by age (trend test), whereas a significantly increased trend by age was found in CG patients (P = 0.0001; trend test); the overall prevalences did not differ significantly between these two groups (OR 1.13; 95%CI 0.95-1.35) (Figure 2, Table 1).

In the subjects representing the POPUL and NoDg groups, the prevalence of IgA antibodies increased by age from the lowest rates (6.5% and 15.1%, respectively) to significantly higher rates in the 55-74-year-old cohorts (52.1% and 45.6%, respectively; P<0.0001; trend test) (Figure 2). The overall prevalence of IgA antibodies was higher in the NoDg patients than that in the POPUL group (OR 1.93, 95%CI 1.73-2.10).

**DISCUSSION**

In the present study, we analyzed, according to age cohorts, a large body of serological data collected during a 15-year period. DGD subjects with gastric disorders known to be associated with *H pylori* infection showed a high and rather a constant prevalence of *H pylori* IgG antibodies in all the 20-year age cohorts. Based on the prevalence of IgA antibodies, the DGD group could be divided into two categories: in GU-CA-category, the age-adjusted IgA prevalences ranged from 78% to 91%; whereas in DU-

![Figure 2](image-url)  
*Figure 2  Prevalence of *H pylori* IgA antibodies by 20-year age cohorts in the Finnish population and patients with different gastric disorders. (Only cohorts including at least 50 subjects are shown.)*
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