

Association of autoimmune type atrophic corpus gastritis with *Helicobacter pylori* infection

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atrophy, as demonstrated by histology and serum markers, and no evidence for an ongoing *H. pylori* infection, eight showed *H. pylori* antibodies by immunoblotting. All eight had elevated PCA and 4/8 also had IF antibodies. Of the six immunoblot-negative patients with severe corpus atrophy, PCA and IF antibodies were detected in four. Among the patients with low to moderate grade atrophic gastritis (all except one with an ongoing *H. pylori* infection), serum markers for gastric atrophy and autoimmunity were seldom detected. However, one *H. pylori* negative patient with mild atrophic gastritis had PCA and IF antibodies suggestive of a pre-atrophic autoimmune gastritis.

CONCLUSION: Signs of *H. pylori* infection in autoimmune gastritis, and positive autoimmune serum markers in *H. pylori* gastritis suggest an etiological role for *H. pylori* in autoimmune gastritis.

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Key words: *Helicobacter pylori*; Autoimmune gastritis; Gastric atrophy; Vitamin B12 deficiency

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Abstract

AIM: To study the association between *Helicobacter pylori* (*H. pylori*) infection and autoimmune type atrophic gastritis.

METHODS: Twenty-three patients with different grades of atrophic gastritis were analysed using enzyme immunoassay-based serology, immunoblot-based serology, and histology to reveal a past or a present *H. pylori* infection. In addition, serum markers for gastric atrophy (pepsinogen I, pepsinogen I/II and gastrin) and autoimmunity [parietal cell antibodies (PCA), and intrinsic factor (IF), antibodies] were determined.

RESULTS: Of the 14 patients with severe gastric

INTRODUCTION

Autoimmune type corpus gastritis, formerly named type

A gastritis, is severe atrophy of gastric corpus associated with hypochlorhydria^[1]. Even without total gastric atrophy, many of these patients have an inability to absorb vitamin B12 from food^[2]. Generally, 15%-20% of vitamin B12 malabsorption in elderly patients is due to pernicious anaemia, as defined as deficiency of intrinsic factor (IF)^[3]. Over 90% of patients with pernicious anaemia have parietal cell antibodies (PCA) and 50%-70% have elevated IF antibodies^[1]. The autoantigen for PCA is H+/K+-adenosine triphosphatase, the proton pump^[4].

In patients with *Helicobacter pylori* (*H. pylori*) infection, superficial gastritis proceeds to atrophic gastritis in about half of the patients^[5]. Although this type of atrophic gastritis, which is associated with intestinal metaplasia, mainly involves the antrum, it can proceed to the corpus or affect the mucosa focally, *viz.* multifocal atrophic gastritis. Advanced atrophy develops over many years and *H. pylori* disappears from the gastric mucosa. In some patients, the antral intestinal metaplasia disappears and PCA appears; thus, the disease resembles classic autoimmune gastritis^[6]. Gastric H+/K+-ATPase is also the major autoantigen in chronic *H. pylori* induced atrophic gastritis in corpus mucosa^[7].

In *H. pylori* induced atrophic gastritis, the activated CD4+ Th1 cells infiltrating the gastric mucosa cross-recognize the epitopes of the gastric parietal cell proton pump and various *H. pylori* proteins^[8,9]. It is not known if *H. pylori* is the initiating factor in activating Th1 cells, which leads to inflammation and apoptosis, or is only a coincidental bystander^[10]. If the classic autoimmune type gastric atrophy is an end-stage of *H. pylori* induced gastric autoimmunity with atrophic gastritis, the prevalence of pernicious anaemia should decrease with declining prevalence of *H. pylori*. It is not known if vitamin B12 malabsorption in the late stages of gastric atrophy could be restored or prevented if *H. pylori* were eradicated earlier^[11-14].

In the present study we investigated the signs of a previous *H. pylori* infection in patients with different grades of atrophic gastritis to assess the proportion of gastric atrophy not associated with *H. pylori* infection.

MATERIALS AND METHODS

All patients with an earlier gastroscopy reprint available and who had undergone a gastroscopy for clinical indications at Herttoniemi Hospital during 2004 and 2005^[15] were included in the present study if their follow-up histology indicated they had atrophic gastritis. Twenty-three of the 38 patients with different grades of atrophic gastritis had a blood sample available and were included in the study. The median age was 65 years and 18 were females.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study and all the participants gave their written informed consent.

Histology

Two biopsies from each of the antrum and the corpus

were taken during gastroscopy and stained with haematoxylin-eosin, Alcian blue (pH 2.5)-periodic acid Schiff, and modified Giemsa stains. All the samples were examined by one pathologist who was unaware of the identity of the samples. The samples were assessed according to the updated Sydney system^[16].

Serum tests

H. pylori antibodies were detected by an enzyme immunoassay (EIA) and by immunoblotting. Serum samples were taken after gastroscopy and stored (-20°C) until analyzed for IgG antibodies to *H. pylori* using a locally validated in-house EIA with high sensitivity and specificity^[17]. Immunoblotting was performed by MP Diagnostics Helico blot 2.1 (MP Biomedicals, Singapore). The interpretation criteria for an *H. pylori* seropositive sample, according to the manufacturer, were: (1) fulfilling the criteria for CagA positivity; (2) the presence of any bands at 89 kDa, 37 kDa, or 35 kDa; or (3) the presence of both the bands at 30 kDa and 19.5 kDa. The criteria for CagA positivity were the presence of 116 kDa CagA band (a) in combination with current infection marker CIM; (b) in combination of the 30 kDa (UreA) and 19.5 kDa bands; or (c) in combination of at least one of the following bands 89 kDa (VacA), 37 kDa, or 35 kDa.

PCA were measured by Varelisa (Pharmacia Diagnostics, Freiburg, Germany) using H+/K+-ATPase as an antigen. According to the manufacturer's instructions, values > 15 U/mL were interpreted as positive but equivocal values (10-15 U/mL) were interpreted negative as well as values < 10 U/mL.

Serum IF antibodies of the blocking type were measured routinely with the haemoglobin charcoal adsorption assay. The cut off value used was 2 U/L.

Serum pepsinogen I and II and gastrin-17 levels were investigated with Gastropanel (Biohit PLC Diagnostics, Helsinki, Finland). The reference ranges were 30-120 µg/L for pepsinogen I, 3-10 µg/L for pepsinogen II, 3-20 for pepsinogen I / II, and 2-10 pmol/L for gastrin-17.

Statistical analysis

The differences between the groups were tested using two-tailed Fisher's exact test and the data were analysed using GraphPad software (QuickCalcs online calculators for scientists www.graphpad.com). *P* values < 0.5 were considered significant.

RESULTS

Of the 23 patients included in the study, 14 had severe gastric atrophy according both to histology and the serum markers, and the remaining nine patients had mild to moderate atrophic gastritis. The patients with severe atrophy were slightly younger (median age 64 years) than the other patients (median age 70 years). None of the patients with severe atrophy had either *H. pylori* in histology or elevated *H. pylori* antibodies in the EIA

Table 1 Histological and serum findings in patients with mild to moderate ($n = 9$) and severe ($n = 14$) atrophic changes in the corpus

Findings	Number of patients with atrophic corpus gastritis						P-value
	Grade 1 or 2			Grade 3			
	IB+ ($n = 8$)	IB- ($n = 1$)	Total	IB+ ($n = 8$)	IB- ($n = 6$)	Total	
Chronic corpus gastritis	7	1	8	8	6	14	NS
Chronic antral gastritis	7	1	8	3	3	6	0.04
Antral intestinal metaplasia	3	0	3	0	0	0	0.05
<i>H. pylori</i> in histology	4	0	4	0	0	0	0.01
Elevated EIA <i>H. pylori</i> IgG ¹	7	0	7	0	0	0	0.0001
Vitamin B12 therapy	1	0	1	4	6	10	0.009
Elevated PCA ²	2	1	3	8	4	12	0.02
Elevated IF antibodies ³	0	1	1	4	4	8	0.04
Low pepsinogen I ⁴	0	0	0	8	6	14	0.0001
Elevated pepsinogen II ⁵	5	0	5	4	1	5	NS
Low pepsinogen I / II ⁶	1	0	1	8	6	14	0.0001
Elevated gastrin-17 ⁷	2	1	3	8	5	13	0.005

¹In-house EIA positive ≥ 700 ; ²Parietal cell antibodies PCA elevated > 15 ; ³Intrinsic factor IF elevated > 2 ; ⁴Pepsinogen I low < 30 ; ⁵Pepsinogen II elevated > 10 ; ⁶Pepsinogen I / II low < 3 ; ⁷Gastrin 17 elevated > 10 . EIA: Enzyme immunoassay; *H. pylori*: *Helicobacter pylori*; PCA: Parietal cell antibodies; IF: Intrinsic factor; NS: Not significant; IB+: Immunoblot positive; IB-: Immunoblot negative. P-value: Total (grade 1 or 2) vs total (grade 3).

(Table 1); one patient had had a successful *H. pylori* eradication therapy 7 years earlier. Of the nine patients with mild to moderate atrophic gastritis, two had had a successful eradication therapy (4 mo and 6 mo earlier, respectively) and four had an ongoing infection shown in histology; seven had elevated *H. pylori* antibodies in the EIA (Table 1). All patients, except one with moderate atrophic gastritis, had chronic gastritis in the corpus, whereas the antrum was significantly less often affected in patients with severe atrophy compared to those with mild and moderate atrophic changes ($P = 0.04$, Fisher's exact test, Table 1). Antral intestinal metaplasia was not found in any of the patients with severe atrophy.

Serum markers for gastric autoimmunity were only rarely detected in patients with mild to moderate atrophic gastritis (PCA in three patients and IF antibodies in one patient, Table 1). In contrast, all 14 patients with severe atrophy had either elevated PCA or IF antibodies, six patients having both antibodies elevated. Furthermore, the levels of elevated PCA and IF antibodies were higher in patients with severe atrophy (eight of 12 patients with elevated PCA had a PCA titre over 100, and the mean IF antibody titre in eight patients with an elevated value was 8.7) compared to patients with only mild to moderate atrophic changes (only one of the three patients with elevated PCA had a PCA titre over 100 and the IF antibody titre in the only patient with an elevated value was 2.1).

H. pylori antibodies could be demonstrated by immunoblotting in 8/9 patients with mild to moderate atrophic gastritis and in 8/14 patients with severe gastric atrophy (Table 1). Patients with severe atrophy and a positive immunoblot result did not significantly differ from those with severe atrophy and negative immunoblot results as far as age, sex, histological findings, and serum results were concerned (Table 1). Although six patients with severe atrophy showed negative immunoblot results

(according to the criteria of the manufacturer) four of them had a positive CagA band in the immunoblot; thus, only two patients showed no evidence of previous *H. pylori* infection. In addition, one patient with mild atrophic gastritis had no evidence (not even a CagA band) for ongoing or previous *H. pylori* infection (Table 1). This particular patient showed clearly elevated PCA (> 100 U/mL) and slightly elevated IF antibodies (2.1 U/L).

DISCUSSION

In our study, of the 14 patients having autoimmune type atrophic gastritis (severe gastric atrophy with elevated PCA and/or IF antibodies) only two had no signs of previous *H. pylori* infection. In addition, all except one of the patients with mild to moderate atrophic corpus gastritis had an ongoing *H. pylori* infection or signs of previous infection. The *H. pylori* negative patient with minor atrophic changes in the gastric corpus had elevated PCA and IF antibodies; whether this particular patient goes on to develop severe gastric atrophy of autoimmune type remains to be shown. To the best of our knowledge, she is the first patient described in the literature as having preatrophic autoimmune gastritis with elevated serum markers of pernicious anaemia and no signs of *H. pylori* infection, despite being investigated with both invasive and non-invasive methods: antrum and corpus histology in two gastroscopies with a 5.4 years interval and negative EIA serology and immunoblotting, including CagA.

In severe gastric atrophy, the exclusion of previous *H. pylori* infection is controversial, as the sensitivity of histology is low^[18], and many of the EIA based serological tests are poorly validated^[19]. In *H. pylori* gastritis, the antibodies in EIA serology decline below the cut-off values along with advanced atrophy^[20], as

well as after eradication therapy^[21]; thus, the previous *H. pylori* infection cannot be deduced by negative EIA serology. Immunoblotting with CagA antibodies can give positive results for years after the disappearance of *H. pylori*^[22,23], but all *H. pylori* strains are not CagA positive. Discrepancies in CagA seropositivity yielded by immunoblotting in patients with severe gastric atrophy^[24,25] may derive from the different sensitivities of the immunoblotting methods used^[26].

Studies of patients with preatrophic autoimmune type of corpus gastritis are rare. In a population-based study, all 12 patients with autoimmune type atrophic gastritis (diffuse lymphocytic infiltration of the entire lamina propria in the corpus mucosa) without severe gastric atrophy showed *H. pylori* in histology or serology^[27]. In the same study, of the 28 individuals with severe autoimmune type gastric atrophy six were *H. pylori* positive in histology and another 13 were positive in serology (altogether 68% positive for *H. pylori*). Considering the moderately high prevalence (2.8% in the Kalixanda study^[27]) of the autoimmune type of gastric atrophy in general, the description in the literature of patients with *H. pylori* negative autoimmune type gastritis in preatrophic stage is rare.

Uibo described a 17-year-old female with no signs of gastritis and *H. pylori* in histology developing atrophic gastritis during a 12-year follow-up^[28]. However, the exclusion of *H. pylori* infection in this case was based only on histology, and the childhood infection rate in this population cohort was nearly 100%. Kuipers described two patients who were negative for *H. pylori* and without gastritis at first visit, who then developed atrophic gastritis (one developed also intestinal metaplasia and pernicious anaemia) during more than 10 years of follow-up^[29]. However, although in this study the *H. pylori* infection was assessed with serology and histology at the first visit, in cases of discrepant results, histology was considered predominant over serology unless atrophic mucosa was observed. Whether these two patients had positive serology at the first visit was not mentioned. In the study of Segni *et al.*^[30] of children with juvenile autoimmune thyroid disease, of the 18 children with elevated PCA who underwent gastroscopy, two children with hypergastrinaemia had *H. pylori* negative preatrophic gastritis, as shown by histology and EIA serology. Immunoblotting was not studied and follow-up has not been published. In the study of adult patients with Sjögren's syndrome, there was no difference in the prevalence of *H. pylori* infection, antigastric antibodies, or gastric histology between patients and controls, but after successful eradication therapy for *H. pylori*, the lymphocytic infiltration and atrophy in patients with Sjögren's syndrome, contrary to the controls, did not improve^[31]. In addition, patients with Sjögren's syndrome who were positive for antigastric antibodies all had *H. pylori* infection and they more often had atrophic gastritis than the controls. In conclusion, from the previous studies, patients with autoimmune type atrophic gastritis without

H. pylori infection might rarely exist, but at the moment a study showing preatrophic gastritis proceeding to total gastric atrophy without *H. pylori* infection is lacking. This is in accordance with our results; as the patient having preatrophic gastritis without signs of *H. pylori* infection did not proceed to total gastric atrophy during 5 years of follow-up.

Several studies suggest that autoimmune atrophic corpus gastritis is associated with *H. pylori* infection in the majority of cases. In one study, two-thirds of patients with atrophic corpus gastritis had evidence of *H. pylori* infection, when assessed with histology and serology^[32]. In another study, 62% of the patients with pernicious anaemia and severe atrophic corpus gastritis had positive *H. pylori* serology^[33]. In one further study, patients with atrophic corpus gastritis were negative for *H. pylori* in histology and in EIA-serology, but positive when studied by immunoblotting^[25]. In another study of atrophic corpus gastritis, among 111 patients with negative *H. pylori* EIA serology, 95.5% were positive in immunoblotting^[34]. In a study of 10 patients with severe atrophic corpus gastritis, all were *H. pylori* negative in histology and in EIA-serology, and only one was positive in immunoblotting^[24]. However, in this particular study, the immunoblotting method used to measure CagA antibodies was less sensitive than EIA-serology in detecting an ongoing *H. pylori* infection. In the present study, all except three patients had a positive CagA band on the immunoblot, including all EIA-serology positive patients. We have studied the sensitivity and specificity of this particular immunoblotting method previously, with good results^[23]. However, not even the immunoblotting method used in our present study can rule out a previous *H. pylori* infection with 100% certainty, as all *H. pylori* strains are not CagA positive. On the other hand, the common occurrence of *H. pylori* antibodies in patients with autoimmune type of atrophic gastritis could be a random effect, as the *H. pylori* infection rate has been nearly 100% in populations now presenting as the peak age group of autoimmune gastritis. This could also be one explanation why *H. pylori* prevalence studied by immunoblotting in patients with serological markers of autoimmune type gastritis (PCA and IF antibodies) was no different from patients with no such markers in our study.

Thus, it still remains to be shown if *H. pylori* infection is crucial for the development of autoimmune type atrophic gastritis. However, bacterial infections might be important in autoimmune processes, as recently suggested by Torchinsky *et al.*^[35]. In this *in vitro* study, phagocytosis of immune cells infected with bacteria and undergoing apoptosis promoted Th17 cell differentiation, the cell type having a potential role in autoimmunity. Thus, it is tempting to speculate that cells in the gastric mucosa infected with *H. pylori* could trigger an autoimmune response.

In conclusion, atrophic corpus gastritis, including

autoimmune type severe atrophy with vitamin B12 malabsorption, is associated with a longstanding *H. pylori* infection in most cases. There is an urgent need for population-based studies to assess the effect of *H. pylori* eradication on the development of vitamin B12 malabsorption.

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COMMENTS

Background

Autoimmune type atrophic gastritis is a severe gastric atrophy associated with pernicious anaemia with lifelong substitution therapy with vitamin B12. Longstanding *Helicobacter pylori* (*H. pylori*) infection proceeds in about 50% of patients to atrophic gastritis. *H. pylori* infection is much more prevalent than autoimmune type gastritis, and the association of these two conditions is possible without a causal relationship.

Research frontiers

Previous studies have shown that *H. pylori* shares several epitopes with the proton pump, and the β -subunit of this pump is the causative antigen in autoimmune gastritis. In animal models, the passive transfer of these antibodies does not cause disease, but CD4+ T-cells are responsible for the gastritis. Recently, it has been shown that bacterial infection can modify the immune response in the direction seen in autoimmune diseases, i.e. Th17 cell differentiation, thus linking infection and autoimmunity.

Innovations and breakthroughs

It is difficult to differentiate severe end stage *H. pylori* atrophic gastritis and autoimmune type gastric atrophy, because the autoimmune serum markers appear in *H. pylori* gastritis with increasing grade of atrophy, as shown in previous studies and confirmed in our study. The preatrophic stage of autoimmune type gastritis without *H. pylori* infection is an unknown entity. Several patients with autoimmune type gastric atrophy have signs of a previous *H. pylori* infection when studied with sensitive methods and remain positive for years, as shown in this study.

Applications

If *H. pylori* initiates the apoptosis that leads to gastric atrophy and vitamin B12 deficiency, eradication of the bacteria before the development of severe atrophic changes should abolish the development of pernicious anaemia and the need of lifelong vitamin B12 substitution therapy.

Peer review

This is a very interesting paper and asks quite an important question as to whether there is an association between *H. pylori* infection and autoimmune type atrophic gastritis. This work could be accepted after revision.

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