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Clinical Profiles, Endoscopic and Laboratory Features and Associated Factors in Patients with Autoimmune Gastritis

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Key Words

Autoimmune gastritis · Iron/vitamin B_{12} deficiency · Antiparietal cell antibody · Bloating · *Helicobacter pylori*

Abstract

Background/Aims: Autoimmune gastritis (AIG) may predispose to gastric carcinoid tumors or adenocarcinomas and may also cause unexplained iron and/or vitamin B_{12} deficiency. The aims of this study were to explore clinical manifestations, endoscopic findings and laboratory features of patients with AIG. ***Methods:*** 109 patients with AIG were enrolled into the study. In addition to demographic and clinical data, gastric lesions, serum gastrin, vitamin B_{12}, antiparietal cell antibody (APA), current *Helicobacter pylori* status, and anti-*H. pylori* IgG were also investigated. ***Results:*** The mean age of the patients was 53.06 ± 12.7 years (range 24–81; 72 (66.1%) women). The most common main presenting symptom was abdominal symptoms in 51 patients, consultation for iron and/or vitamin B_{12} deficiency in 36, and non-specific symptoms including intermittent diarrhea in 15 patients. Endoscopic lesions were detected in 17 patients, hyperplastic polyps in 8, gastric carcinoid tumor in 4, fundic gland polyps in 3, and adenomatous polyps in 2 patients. *H. pylori* was negative in all patients in biopsy specimens; however, anti-*H. pylori* IgG was positive in 30 (27.5%) patients. 91 patients (83.4%) were positive for APA. ***Conclusion:*** In patients with AIG, the main symptoms prompted for clinical investigation were: abdominal symptoms, iron/B_{12} deficiency and non-specific symptoms. 20% of patients with AIG had various gastric lesions including type I gastric carcinoids. None of the patients were positive for *H. pylori* by means of invasive tests; however, anti-*H. pylori* IgG was found in 27.5% of patients. Patients referring with non-specific abdominal symptoms such as bloating, diarrhea and iron/B_{12} deficiency should be investigated for the presence of AIG.

Introduction

Autoimmune gastritis (AIG) is an organ-specific inflammatory autoimmune disease characterized by loss of gastric parietal cells and formation of autoantibodies against some molecules containing H^+,K^+-ATPase and intrinsic factor which causes impaired metabolism of vitamin B_{12} and sometimes iron deficiency anemia. Histo-

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logically, AIG is characterized by a chronic inflammatory infiltration affecting mainly the corpus mucosa of the stomach causing loss of parietal cells [1, 2]. The prevalence of AIG is more prevalent in Scandinavian countries, in which it accounts for up to 5% of patients with chronic gastritis; however, 1.9% of Western populations over the age of 60 years have AIG [3, 4]. On the contrary, AIG is a rare disease in South America or Asia [5] in which a high prevalence of *Helicobacter pylori* infection exists [6, 7]. AIG patients have an increased risk of developing gastric cancer and neuroendocrine tumors [8, 9]. The incidence of developing gastric cancer rates ranges from 1 to 3% for gastric carcinoma and from 1 to 7% for carcinoid tumors [10–12]. Mainly studies investigating the incidence of gastric cancer in AIG were performed on patients with pernicious anemia. As a consequence, the risk for cancer development has been linked to the presence of pernicious anemia. However, it has been demonstrated that AIG can also occur with other hematological disorders such as iron deficiency anemia [13]. AIG is clinically 'silent' in the early stages of the disease and there is no specific symptom related to this disease causing delay in the diagnosis, thus diagnosis is merely limited to clinical suspicion. Since AIG is an asymptomatic disease, early diagnosis of AIG is important because AIG carries a risk for pernicious anemia, iron deficiency anemia and it is associated with an increased risk for gastric (pre)malignant lesions. For this reason, the aims of the present study were to determine clinical manifestations, endoscopic and laboratory features and associated factors in patients with AIG.

Materials and Methods

Patients

In this study, a total of 109 patients with AIG were enrolled into the study. The diagnosis of AIG was based on the histopathological findings in gastric biopsy tissue; histologically, AIG is characterized by a chronic inflammatory infiltrate accompanied by loss of oxyntic glands, parietal and zymogenic cells affecting predominantly the fundus and corpus of the stomach [14]. Moreover, serum gastrin level, presence of antiparietal cell antibody (APA) and gastric juice pH were also investigated in each patient as described by Vargas et al. [15]. Demographic data of each patient including age, gender, presence of concomitant autoimmune diseases and main complaint prompted for clinical investigation were noted. The present study was approved by the Institutional Review Board of Ankara University Faculty of Medicine and written informed consent was obtained from all participants.

Gastroscopic Examinations

Endoscopy was done in all patients. Endoscopic examinations were performed using a standard gastroscope (Fujinon, Fuji Photo Optical Co., Tokyo, Japan) after overnight fasting with special emphasis on gastric macroscopic lesions. Findings were described according to the global impression on the presence of any macroscopic lesion and the presence of gastric atrophy. Gastric atrophy was decided by the visualization of the submucosal vessels because of the thinning of the mucosa in the corpus of the stomach [16].

Laboratory Tests

A venous blood sample was drawn from each patient in order to evaluate vitamin B_{12}, iron, serum gastrin, APA and anti-*H. pylori* IgG after overnight fasting. Routine hematological and biochemical tests were measured by standard laboratory procedures. Serum gastrin level (Biosource Europe, Nivelles, Belgium, with radioimmunoassay according to the instructions of the supplier) and the presence of APA (Euroimmun, Lübeck, Germany, with an indirect immunofluorescence test according to the instructions of the supplier) were also investigated in each patient. *H. pylori* status was determined by both histopathological evaluation and serologic testing. Serum *H. pylori* IgG was measured with enzyme-linked immunosorbent assay (ELISA; Trinity Biotech, Jamestown, N.Y., USA). Serum vitamin B_{12} and folate concentrations were determined using a chemiluminescence flow system (Beckman Access Method; Beckman Coulter Inc., Brea, Calif., USA). The diagnosis of vitamin B_{12} deficiency was based on serum vitamin B_{12} levels <200 pg/ml [17, 18].

Statistical Analysis

Statistical evaluation was performed with SPSS 16.0 for Windows (SPSS Inc., Chicago, Ill., USA). All values were defined as mean $\pm$ SD unless stated otherwise. A two-tailed t-test was used to compare quantitative variables. Fisher's exact test and Mann-Whitney test were used for statistical comparisons as appropriate. A p value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of Patients

The mean age of the patients with AIG was 53.0 $\pm$ 12.7 years (range 24–81; 72 women, female:male ratio 1.95). Abdominal symptoms (group 1, n = 51, 46.7%) was the symptom seen most frequently. The reason for investigation in 36 patients (group 2, 33%) was iron/B_{12} deficiency who were referred from other departments, and symptoms that prompted investigation were non-specific symptoms in 22 patients (group 3, 20.1%) (table 1). 15 patients were smokers. 34 (31.2%) patients also carried other autoimmune diseases: 21 had autoimmune thyroid disease, 3 had diabetes mellitus, 2 had autoimmune thyroid disease and diabetes mellitus, 2 had celiac disease, 2 had rheumatoid arthritis, 1 had vitiligo, 1 had myasthenia gravis, 1 had autoimmune hemolytic anemia, and 1 pa-

Table 1. Clinical symptoms and symptom subgroups of patients with AIG that prompted investigation

Main symptom	Symptom subgroups	n
Group 1: abdominal symptoms (n = 51)	abdominal bloating only	32
	abdominal bloating + abdominal pain	13
	abdominal bloating + nausea	5
	abdominal bloating + constipation	1
Group 2: iron/B_{12} deficiency (n = 36)	iron deficiency	18
	B_{12} deficiency	16
	iron + B_{12} deficiency	2
Group 3: non-specific symptoms (n = 22)	check-up	7
	intermittent diarrhea	7
	belching	3
	nausea	2
	fatigue	2
	amnesia	1

tient had Sjögren's syndrome. When these three groups were compared with each other, no significant difference was found in terms of mean age, gender, BMI, accompanying autoimmune disease, gastrin, and APA positivity (table 2).

Laboratory and Endoscopic Features of AIG Patients

Mean serum gastrin and vitamin B_{12} levels were 1,310.93 ± 699.14 and 185.71 ± 120.58 pg/ml, respectively. Among 109 AIG patients, 91 (83.4%) were APA-positive and 18 (16.51%) were APA-negative. None of the patients were positive for *H. pylori* infection in the histopathological examination; however, 30 patients (27.5%) were found to be positive for *H. pylori* by means of serologic testing. The number of serologic *H. pylori*-positive patients in group 2 was higher compared to patients in group 1 (17/36 vs. 10/51, p = 0.06) and group 3 (17/36 vs. 3/22, p = 0.09). Laboratory features of AIG patients are shown in table 2. When AIG patients were analyzed by means of laboratory features, B_{12} deficiency was found in 88 patients and iron deficiency in 85 patients. When AIG patients with B_{12} deficiency were compared with those without B_{12} deficiency, there were no differences in terms of mean gastrin level (p = 0.909), *H. pylori* (p = 0.791) and APA positivity (p = 0.318). When the patients with iron deficiency were compared with those without iron deficiency, no difference was found in terms of mean gastrin level (p = 0.151), mean serum B_{12} level (p = 0.250), *H. pylori* (p = 0.064) and APA positivity (p = 0.494). Serum vitamin B_{12} level was lower in group 2 patients compared to group 1 patients (147.11 vs. 200 pg/ml, p = 0.013) and group 3 patients (147.11 vs. 212.70 pg/ml, p = 0.05) (table 2). Gastric lesions were observed in 17 (15.5%) patients endoscopically (hyperplastic polyp in 8, gastric carcinoid tumor type I in 4, fundic gland polyp in 3, and adenomatous polyps in 2 patients). No gastric endoscopic lesion was found in AIG patients who were younger than 40 years of age; patients with gastric lesions were all older than 40 years (p = 0.037). In addition, no correlation was found between presence of gastric lesions and APA positivity (p = 0.296), *H. pylori* (p = 0.236), iron deficiency (p = 0.455), B_{12} deficiency (p = 0.187), BMI (p = 0.119), gender (p = 0.267), accompanying autoimmune diseases (p = 0.771), smoking (p = 0.795), and serum gastrin level (p = 0.896). Gastric endoscopic lesion frequency was found to be higher in patients in group 2 compared with patients in group 3 (9/36 vs. 0/22, p = 0.011) and found to be higher in patients in group 1 compared with patients in group 3 (8/51 vs. 0/22, p = 0.049). Gastric food retention, as determined by gastric remnants of food seen during endoscopic examination after at least 12 h of fasting [19], was found in 4 patients (3 patients in group 1 and 1 patient in group 3). The mean serum gastrin level of these 4 patients was >1,000 pg/ml (p = 0.016); however, there were no statistically meaningful difference in terms of age (p = 0.127), B_{12} (p = 0.229), iron (p = 0.371), ferritin (p = 0.310), BMI (p = 0.444), folate (p = 0.943), *H. pylori* (p = 0.798), APA positivity (p = 0.520), smoking (p = 0.452) and presence of endoscopic lesions (p = 0.502) compared to other AIG patients.

Evaluation of AIG Patients in Terms of APA and H. pylori *status*

Among 109 AG patients, 91 (83.4%) were APA-positive and 18 (16.51%) were APA-negative. APA-positive patients were younger (51.77 ± 12.44 vs. 60.53 ± 0.31, p = 0.021) and smoking rate (9/91 (6.5%) vs. 6/18 (33.3%), p = 0.017) was higher compared to APA-negative patients. Among APA-positive AIG patients, *H. pylori* positivity [27/91 (29.6%) vs. 3/18 (16.6%), p = 0.259)] was higher but this difference was not statistically significant. There was no difference between APA-positive and APA-negative patients in terms of BMI, accompanying autoimmune diseases, main complaint, presence of carcinoid tumor, serum gastrin, B_{12}, and ferritin (table 3). Anti-*H. pylori* IgG was positive in 30 (27.5%) patients. There was no difference between *H. pylori*-positive and *H. pylori*-negative patients in terms of BMI, accompanying autoimmune diseases, main complaint, presence of carcinoid tumor, serum gastrin, B_{12}, and ferritin (table 4).

Table 2. Demographic, laboratory and clinical features and comparison of these parameters according to the symptom groups

	Group 1: abdominal symptoms	Group 2: iron/B_{12} deficiency	Group 3: non-specific symptoms	p
Number	51 (46.7%)	36 (33%)	22 (20.1%)	
Mean age, years	51.81 ± 12.39	54.65 ± 14.83	53.73 ± 10.66	[1]0.395, [2]0.820, [3]0.560
Females	32	26	14	[1]0.336, [2]0.493, [3]0.942
Gastrin, pg/ml	1,314	1,288	1,340	[1]0.867, [2]0.776, [3]0.889
B_{12}, pg/ml	200	147.11	212.70	[1]0.013, [2]0.05, [3]0.730
Smoking	7	5	3	[1]0.983, [2]0.987, [3]0.992
Presence of accompanying autoimmune diseases	13	12	9	[1]0.395, [2]0.614, [3]0.188
Presence of gastric lesions	8	9	0	[1]0.281, [2]0.011, [3]0.049
Anti-*H. pylori* IgG	10	17	3	[1]0.06, [2]0.09, [3]0.541
APA	43	31	17	[1]0.817, [2]0.387, [3]0.471
Gastroparesis	3	0	1	[1]0.264, [2]0.197, [3]0.818

Figures represent numbers of patients unless indicated otherwise.
[1] Comparison between groups 1 and 2. [2] Comparison between groups 2 and 3. [3] Comparison between groups 1 and 3.

Table 3. Association between symptoms, clinical and laboratory parameters and APA positivity

	APA-positive AIG patients	APA-negative AIG patients	p
Number	91	18	
H. pylori-positive	27	3	0.259
<40 years	20	1	0.106
Age, years	51.77 ± 12.44	60.53 ± 0.31	0.021 (95% CI –16.18 to –1.34)
Smoking	9	6	0.017
Females	63	9	0.115
Gastrin, pg/ml	1,328.4 ± 702.606	1,222.1 ± 694.20	0.558 (95% CI –252.29 to 464.94)
B_{12}, pg/ml	177.72 ± 107.43	228.06 ± 172.81	0.115 (95% CI –113.12 to 12.43)
Gastroparesis	3	1	0.641
Presence of gastric lesions	16	1	0.199
Presence of accompanying autoimmune diseases	28 iron/B_{12} deficiency: 31 abdominal symptoms: 43 non-specific symptoms: 17	6 iron/B_{12} deficiency: 5 abdominal symptoms: 8 non-specific symptoms: 5	0.853 0.663

Figures represent numbers of patients unless indicated otherwise.

Age and Gender Associations of AIG Patients

Patients older than 40 years and those younger than 40 years were compared. Age 40 was chosen because no gastric endoscopic lesion was observed under 40 years of age. Of the AIG patients, 21 (19.3%) were <40 years of age while 88 (80.7%) were >40. When older and younger patient groups were compared, no significant differences were found for gastrin (p = 0.754), mean B_{12} levels (p = 0.213), *H. pylori* positivity (p = 0.905) and APA positivity (p = 0.187). 72 female and 37 male AIG patients were eval-

Table 4. Association between symptoms, clinical and laboratory parameters and *H. pylori* status

	Serologic *H. pylori*-positive AIG patients	Serologic *H. pylori*-negative AIG patients	p
Number	30	79	
<40 years	6	15	0.905
Age, years	54.40 ± 14.14	53.28 ± 12.35	0.781 (95% CI –7.15 to 5.39)
Smoking	2	13	0.229
Females	18	54	0.411
Gastrin, pg/ml	1,233 ± 471	1,340.5 ± 768.73	0.411 (95% CI –405.36 to 190.45)
B_{12}, pg/ml	187 ± 89.53	185.19 ± 130.77	0.941 (95% CI –50.29 to 54.20)
Gastroparesis	1	3	0.908
Presence of gastric lesions	7	10	0.170
APA-positive	27	64	0.388
Presence of accompanying autoimmune diseases	9 iron/B_{12} deficiency: 17 abdominal bloating: 10 non-specific symptoms: 3	25 iron/B_{12} deficiency: 19 abdominal bloating: 41 non-specific symptoms: 19	0.837 0.05

Figures represent numbers of patients unless indicated otherwise.

uated in this study. When female AIG patients were compared with male AIG patients, the mean gastrin level was higher in female patients compared to male patients (1,413.80 ± 722.57 vs. 1,110.6 ± 611.79 pg/ml, p = 0.031). The mean homocysteine level was higher in male patients (13.51 ± 5.24 vs. 10.24 ± 2.59 μmol/l, $p < 0.05$). The smoking rate was higher in male patients compared to female patients (6/72 vs. 9/37, p = 0.037). There were no significant differences in terms of mean age (p = 0.071), APA positivity (p = 0.172), mean BMI (p = 0.644), accompanying autoimmune diseases (p = 0.828), and B_{12} level (p = 0.871).

Discussion

This study represents one of the larger populations of patients with AIG investigating clinical and demographic parameters. Little information is available regarding clinical manifestations and demographic characteristics of this condition. In the present study we have demonstrated that this disorder is more common in females (66%). Abdominal bloating-related symptoms and iron/vitamin B_{12} deficiency are the most frequent conditions leading patients to seek medical attention following non-specific symptoms including intermittent diarrhea. Purdy et al. [20] analyzed 56 patients and found similar results in their study. The median age of their patients was 62 years, and 74% were female. They also reported that 14 had a history of B_{12} deficiency, 5 had no previous diagnosis of AIG and 21 patients also had no history relevant to AIG. Pain was the most frequent symptom in these patients (29%). However, they did not explain in detail other symptoms in the rest of the patients. In our study, pain was associated with abdominal bloating. 41 out of 109 (37.6%) patients had various other autoimmune diseases, mainly thyroid disorders and diabetes mellitus. Lahner et al. [21] investigated 319 atrophic body gastritis patients by means of autoimmune thyroid diseases and they found that 128 patients also had autoimmune thyroid diseases. In their study, female sex, presence of parietal cell antibody and presence of metaplastic atrophy were risk factors for having autoimmune thyroid disease.

In our study, among 109 AIG patients, 91 (83.4%) were APA-positive and 18 (16.51%) were APA-negative. APA-positive patients were younger and smoking rate was higher. Among APA-positive AIG patients, female ratio and *H. pylori* positivity were higher but this difference was not statistically meaningful. Centanni et al. [22] investigated 22 patients with AIG and they reported that APA was positive in 68% (15/22) of the AIG patients. In another study, Lahner et al. [23] studied 165 patients with

chronic atrophic gastritis and 113 controls by means of APA and intrinsic factor antibody and found APA in 81% of patients and 10% of controls and intrinsic factor antibody in 27% of patients. APA can be found in *H. pylori*-related gastritis and also found in up to 10% of normal healthy subjects. However, APA positivity is not specific for AIG. In our study, APA-positive patients were younger (51.77 ± 12.44 vs. 60.53 ± 0.31, p = 0.021) and smoking rate (9/91 (6.5%) vs. 6/18 (33.3%), p = 0.017) was higher compared to APA-negative patients. We did not demonstrate any association between APA positivity and clinical parameters. Its presence may indicate an autoimmune origin.

In the current study, there was no evidence for an ongoing *H. pylori* infection as investigated by pathology; however, anti-*H. pylori* IgG was positive in 30 (27.5%) of the patients. There was no difference between *H. pylori*-positive and *H. pylori*-negative patients in terms of BMI, accompanying autoimmune diseases, main complaint, serum gastrin, B_{12}, and ferritin. Annibale et al. [24] reported that two-thirds of patients with atrophic corpus gastritis had evidence of *H. pylori* infection, when assessed with serology and histology. In another study by the same group, they found that 62% of patients with atrophic corpus gastritis and pernicious anemia had positive *H. pylori* serology [25]. However, Mini et al. [26] found that in 111 patients with atrophic corpus gastritis with negative *H. pylori* serology, 95.5% were positive in immunoblotting. We did not have an opportunity to study our patients with this technique. Erdogan and Yılmaz [27] investigated the relationship between *H. pylori* and gastric autoimmunity. They studied 82 *H. pylori*-positive and 96 *H. pylori*-negative dyspeptic patients. In this study, 11 (13.4%) *H. pylori*-positive and 14 (14.6%) *H. pylori*-negative patients were found to be APA-positive. They did not find any significant relationship between *H. pylori* and APA positivity. In view of these findings, bacterial infection may be an important autoimmune process in the development of AIG. Torchinsky et al. [28] in their in vitro study suggested that apoptosis and phagocytosis of bacteria-infected immune cells promoted Th17 cell differentiation. Th17 cells have a potential role in the development of autoimmunity. In this context, it is attractive to speculate that *H. pylori* infection could trigger an autoimmune response in the gastric mucosa.

Park et al. [29] analyzed endoscopic lesions of 461 patients with AIG. Of these patients, 143 had 240 gastric endoscopic lesions (179 polyps, 46 gastric carcinoids, 11 adenocarcinomas, 3 lymphomas, and 1 gastrointestinal stromal tumor) and they concluded that patients with AIG are very likely to develop neoplasms and polyps. In our patients, we identified gastric lesions in 17 (15.5%) (hyperplastic polyp in 8, gastric carcinoid tumor type I in 4, fundic gland polyp in 3, and adenomatous polyps in 2 patients). In this study, no gastric endoscopic lesion was found in AIG patients who were younger than 40 years of age; patients with gastric lesions were all older than 40 years. In addition, we did not find any correlation between the presence of gastric lesions and demographic and laboratory parameters studied. The number of gastric endoscopic lesions was found to be higher in patients in group 2 (iron/B_{12} deficiency) compared with patients in group 3 (9/36 vs. 0/22, p = 0.011). This finding is not surprising because gastric lesions may cause iron deficiency. Interestingly, gastric food retention was found in 4 patients (3 in group 1 and 1 in group 3). This finding may cause bloating, therefore it is useful to apply a gastric emptying study for patients with bloating in order to identify gastroparesis and which patients need prokinetic therapy.

In the present study there are several potential limitations. First, we have limited data regarding the previous *H. pylori* eradication therapies of all patients. Second, only 30 patients (biopsy-negative, serology-positive) received triple eradication therapy including lansoprazole 30 mg bid, amoxicillin 1,000 mg bid and clarithromycin 500 mg bid for 2 weeks. Furthermore, 18 out of 30 patients had ^{13}C urea breath test results and all were negative; however, we do not provide data regarding ^{13}C urea breath test results of the remaining 12 patients. These results create difficulty in drawing a conclusion from pathology-negative, serology-negative patients whether they have never been infected by *H. pylori* or not.

In conclusion our data indicated that most of the patients with AIG are female and coexistence with other autoimmune disorders is not uncommon. Although clinical manifestations of this group are heterogeneous the majority of patients seek medical attention due to abdominal bloating-related symptoms and iron and/or vitamin B_{12} deficiency. Physicians should be aware of the heterogeneity of the clinical manifestations of this condition, therefore female patients with iron/B_{12} deficiency and/or abdominal bloating-related symptoms should be considered and, since several types of gastric lesions may develop in patients with AIG, it is important to recognize AIG in daily practice.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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