Role of autoimmune gastritis, *Helicobacter pylori* and celiac disease in refractory or unexplained iron deficiency anemia

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Background and Objectives. Conventional endoscopic and radiographic methods fail to identify a probable source of gastrointestinal blood loss in about one third of males and post-menopausal females and in most women of reproductive age with iron deficiency anemia (IDA). Such patients, as well as subjects refractory to oral iron treatment, are often referred for hematologic evaluation.

Design and Methods. We prospectively studied 150 consecutive IDA patients referred to a hematology outpatient clinic, screened for non-bleeding gastrointestinal conditions including celiac disease (antiendomysial antibodies), autoimmune atrophic gastritis (hypergastrinemia with strongly positive antiparietal cell antibodies) and *H. pylori* infection (IgG antibodies confirmed by urease breath test).

Results. The mean age of all subjects was 39±18 years and 119 of the 150 patients were female. We identified 8 new cases of adult celiac disease (5%). Forty IDA patients (27%) had autoimmune atrophic gastritis of whom 22 had low serum vitamin B12 levels. *H. pylori* infection was the only finding in 29 patients (19%), but was a common co-existing finding in 77 (51%) of the entire group. Refractoriness to oral iron treatment was found in 100% of patients with celiac disease, 71% with autoimmune atrophic gastritis, 68% with *H. pylori* infection, but only 11% of subjects with no detected underlying abnormality. *H. pylori* eradication in previously refractory IDA patients in combination with continued oral iron therapy resulted in a significant increase in hemoglobin from 9.4±1.5 (mean ± 1SD) before treatment to 13.5±1.2 g/ dL ($p<0.001$ by paired t test) within 3 to 6 months of treatment.

Interpretation and Conclusions. The recognition that autoimmune atrophic gastritis and *H. pylori* infection may have a significant role in the development of unexplained or refractory IDA in a high proportion of patients should have a strong impact on our daily practice of diagnosing and managing IDA.

Key words: iron deficiency, celiac disease, *Helicobacter pylori*, atrophic gastritis, vitamin B12 deficiency.

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Spontaneous iron excretion in adult subjects is minimal and iron deficiency anemia (IDA) is generally attributed to abnormal blood loss.[1] This may be caused by gastrointestinal bleeding or, in young females of reproductive age, by increased menstrual flow and the increased requirements of pregnancy. However, in adult males and post-menopausal females, major studies evaluating the gastrointestinal tract for IDA employing endoscopic and radiographic methodologies have only been able to identify a probable source of upper or lower gastrointestinal bleeding in about 62 to 64% of patients.[2,3] Similarly, no evidence of gastrointestinal blood loss can be found in the vast majority of young, fertile females with IDA. Such patients with a low likelihood of gastrointestinal blood loss, and patients refractory to oral iron treatment are often referred for hematologic evaluation. In recent years, there has been an increasing awareness of subtle, non-bleeding gastrointestinal conditions that may result in abnormal iron absorption leading to IDA in the absence of gastrointestinal symptoms. Thus, the importance of celiac disease as a possible cause of IDA refractory to oral iron treatment, without other apparent manifestations of malabsorption syndrome[4-10] is increasingly being recognized. In addition, *Helicobacter pylori* infection has been implicated in several recent studies as a cause of IDA refractory to oral iron treatment with a favorable response to *H. pylori* eradication.[11-17] Likewise, achlorhydric gastric atrophy or autoimmune atrophic gastritis, a condition associated with chronic idiopathic iron deficiency, has been shown to be responsible for refractory IDA in over 20% of

patients with no evidence of gastrointestinal blood loss.[18-20] Although achylia gastrica, a condition indistinguishable from autoimmune atrophic gastritis, was defined by Faber as a distinct clinical entity responsible for IDA as early as 1909[21] and extensively studied subsequently by Wintrobe and others,[22-25] this entity was almost completely forgotten and largely ignored in major studies of IDA.[2,3]

The recent availability of convenient, non-invasive screening methods for identifying celiac disease, autoimmune atrophic gastritis and *H. pylori* gastritis, has greatly facilitated the recognition of patients with these entities, resulting in an increased awareness of these conditions and their possible role in the causation of IDA.[18,19] Unlike IDA patients referred for evaluation of possible gastrointestinal bleeding in whom the causes of anemia are well documented, our knowledge of underlying conditions responsible for IDA in patients referred for hematologic evaluation with no apparent gastrointestinal disease is limited. The objective of the present study was to establish, in a systematic and prospective manner, the cause of IDA among patients referred for evaluation to a community hematology clinic over a period of two years with particular emphasis on non-bleeding gastrointestinal causes of IDA, employing non-invasive serological screening tests supplemented by currently accepted diagnostic methodologies.

Design and Methods

Target population

The population for this prospective study consisted of patients with IDA and a low apparent likelihood of gastrointestinal disease referred by family physicians to a community hematology clinic. All the patients had received oral iron treatment prior to referral and many were described as refractory to oral iron therapy. All newly referred patients with IDA were included, starting from September 1, 2001, for a period of 2 years, if their hemoglobin at referral was 11 g/dL or less, and if they fulfilled the following criteria for iron deficiency anemia: mean corpuscular volume (MCV) less than 80 fL, transferrin saturation less than 15%, and serum ferritin less than 12 μg/L (143 patients) or two of the above and an increase in hemoglobin > 1.0 g/dL in response to iron therapy (7 patients). Although patient recruitment was terminated in September 2003, follow-up visits were continued allowing a follow-up period of at least 6 months from presentation. This prospective study was approved by the Institutional Ethics Committee of Shaare Zedek Medical Center.

The control group of 60 non-anemic subjects was recruited from among asymptomatic and apparently healthy subjects of comparable age (see below) and gender (9 males and 51 females) referred within the same period for evaluation of minor problems such as suspected thrombophilia without evidence of thrombosis (n=44), no disease (n=10) or borderline white blood cell counts (n=6).

Laboratory methods

Complete blood counts (CBC) were performed by a SysmexSE-9000 automated analyzer (KOBE, Japan) calibrated daily with standards provided by the manufacturer. Routine biochemical measurements including serum iron (normal range 59-158 μg/dL), total iron binding capacity (TIBC; normal range 226-338 μg/dL) and serum ferritin (normal range males 40-340, females 14-150 μg/L) were performed by a Hitachi 747 automated analyzer with quality control assurance by UKNEQAS (Birmingham, UK). Fasting serum B_{12} levels were determined by the ADVIA Centaur VB_{12} assay which is an automated competitive immunoassay using direct chemiluminescent technology. The lower limit of normal was defined as <181 ng/L. Fasting serum gastrin levels were determined by GammaDab® Gastrin ^{125}I RIA Kit (DiaSorin, Stillwater Minnesota, USA) and expressed as pg/mL, normal limits < 107. For the detection of IgG antibodies to *H. pylori* in human serum, the IMMULITE® 2000 *H. pylori* IgG, a solid-phase chemiluminescent immunometric assay (DPC Diagnostics, Los Angeles, CA, USA) with an analytical sensitivity limit of 0.4 U/mL was used; a value < 0.9 U/mL was considered to be negative. Anti-endomysial IgG and IgA antibodies and anti-gastric parietal cell IgG antibodies (APCA) were determined by an indirect immunofluorescence antibody test for semi-quantitative detection of antibodies using the ImmuGlo™ Anti-Endomysial Antibody Test System (IMMCO® diagnostics, Buffalo, NY, USA). Results were considered positive if equal to or greater than 1:40 dilution. Intrinsic factor antibodies were assayed by enzyme-linked immunoassay (ALPHADIA,® Belgium) detecting type I and type II antibodies. Results exceeding 1.1 were considered positive. Anti-gliadin antibodies were measured by an indirect assay employing peroxidase-labeled rabbit anti-human IgG and IgA antibodies employing the BINDAZYMETM Human Anti-Gliadin IgG and IgA kits (The Binding Site Ltd., Birmingham, UK). Results were considered positive if equal to or more than 10 U/mL for IgG and 5 for IgA antibodies

The ^{13}C-urease breath test was performed as described by Gal *et al.*[26] Briefly, patients were given 75 mg urea labeled with ^{13}C in 200 mL orange juice and breath samples were collected at immediately before (T0') and 30 minutes after (T30') ^{13}C intake. Results were expressed as the difference between the

two scores (δ over baseline). The cut-off $^{13}C/^{12}C$ of T30' minus T0' was 3.5%. Patients were instructed to discontinue treatment with H2 antagonists, proton pump inhibitors or any antibiotics one week before the test. Repeat tests for validation of *H. pylori* eradication were performed at least 1 month after completing triple therapy.

Non-invasive studies

For each newly presenting patient satisfying the above criteria of IDA during the study period, the following assessments were completed and the results prospectively recorded. *Medical history*: gastrointestinal symptoms, results of previous gastrointestinal investigations, blood donation, history of epistaxis or gastrointestinal blood loss, use of aspirin or other non-steroidal anti-inflammatory drugs (NSAID), family history of gastrointestinal disease including cancer, cold intolerance or increased hair loss, dysphagia and brittle nails. Excessive menstrual bleeding was defined as more than two days of heavy bleeding and presence of formed clots. *Physical examination*: brittle or flat nails, pallor, abdominal mass, splenomegaly, mucosal or cutaneous telangiectasiae.

Complete blood count, serum iron, total iron binding capacity, serum ferritin, serum B_{12}, folate, erythrocyte sedimentation rate, fibrinogen and C-reactive protein. Routine biochemistry including serum albumin and cholesterol. Celiac serology: antiendomysial and antigliadin antibodies. *Helicobacter pylori* IgG antibodies. Antiparietal cell antibodies (APCA), and serum gastrin.

Invasive gastrointestinal studies

After completing the initial workup including non-invasive screening for celiac disease, atrophic gastritis and *H. pylori* infection, the following categories of patients were referred for additional invasive gastrointestinal studies: (i) all adult males (n=21), postmenopausal females (n=21) and fertile females with gastrointestinal symptoms or a history of familial cancer (n=6) were referred for full endoscopic investigation including colonoscopy and upper gastrointestinal tract endoscopy except for 5 subjects who had already recently had such studies; (ii) all 8 patients with positive endomysial antibodies were referred for upper gastrointestinal tract work-up, including jejunal biopsies; (iii) upper gastrointestinal endoscopic studies including multiple gastric mucosal biopsies, were also performed in 20 of the 40 patients with hypergastrinemia and positive antiparietal antibodies, and in 6 of the 8 patients aged below 16 years with *H. pylori* infection. Young females with a history of menorrhagia and/or *H. pylori* infection without gastrointestinal complaints and no history of familial cancer and those with a negative diagnostic work-up had 5 occult blood (Hemoccult-II) tests each, and if negative, no gastrointestinal tract studies were considered necessary.

All patients with abnormal titers of *H. pylori* IgG antibodies were referred for a urease breath test for confirmation of *H. pylori* infection. The urease breath test was repeated one month after completing triple therapy.

Interventional studies

Oral iron treatment consisted of essicated ferrous sulphate at a twice daily dose of 50 mg elemental iron. In case of intolerance, the dose was reduced to 50 mg/d. Follow-up visits, including repetition of relevant laboratory tests, were performed at 1-month intervals for the first 3 months, and at 2- to 3-month intervals thereafter. Refractoriness to oral iron treatment was defined as a failure of the hemoglobin to increase by at least 1.0 g/dL after 2 months of treatment. Thirty-one patients received parenteral iron (Iron sucrose, Venofer, Vifor) because of continued refractoriness to oral treatment (n=21), advanced pregnancy (n=7) or personal preference (n=3).

Triple therapy for *H. pylori* eradication consisted of omeprazole 20 mg×2/day, amoxycillin 1 gm×2/day and clarithromycin 500 mg×2/day for 7 days. The method of selection for treatment, number of evaluable patients and their response to triple therapy are described in the *Results* section.

Statistical analysis

The Student t-test was used for continuous variables and the χ^2 test for categorical variables. For continuous variables that were measured before and after interventions, (for example hemoglobin levels) we used a paired t-test. All tests were two-tailed. SPSS 10.0 for windows was used for all the analyses.

Results

Conditions associated with iron deficiency anemia

The age and main conditions associated with IDA in the 150 patients included in the present study are described in Table 1. There were 10 subjects younger than 16 years (6 boys and 4 girls) and 140 between 16 and 77 years (21 males and 119 females). Hypergastrinemia, characterized by grossly increased serum gastrin levels (552±450 [mean±1SD], range 125-1464 pg/mL) in combination with strongly positive (+3 to +4) antiparietal cell antibody titers, was encountered in 40 patients (27%), of whom 34 were females. Four of the 40 subjects with hypergastrinemia were younger than 16 years (3 girls and 1 boy). Of the 40 patients with combined hypergastrinemia

Table 1. Conditions associated with IDA: age and pertinent laboratory findings.

Condition (n)	*Age (years)*	*Hemoglobin g/dL*	*MCV fL*	*Iron mg/dL*	*TIBC µg/dL*	*Ferritin mg/L*	*B_{12} µg/L*	*Gastrin pg/mL*
Hypergastrinemia & APCA (40)	39*±17	9.32±1.11	70.8±8.3	25.0±12.5	336.6±37.0	5.4±5.7	225.7±130.1	551.5±450.4
H. pylori ** (29)	38±16	9.03± 1.30	68.1±8.5	21.7±9.3	356.1±54.9	4.5±4.0	297.0±101.9	85.9±56.6
Menorrhagia (37)	37±11	9.03± 1.12	71.4±6.7	27.6±13.7	358.3±54.1	5.9±5.0	271.5±107.1	61.4±18.4
Gastrointestinal lesions (26)	59±19	9.37±1.18	75.2±9.4	24.9±9.9	341.7±44.0	9.8±18.8	380.9±344.6	89.3±47.1
Celiac disease (8)	38±12	9.29±1.18	69.9±7.6	22.4±9.9	358.6±56.9	3.4±1.9	213.7±79.3	64.5±28.2
Negative (10)	33±17	9.33±1.17	71.6±5.8	23.6±10.7	341.3±37.9	6.8±7.3	266.3±117.9	61.0±32.0
Total (150)	39±18	9.13±3.06	69.0±14.4	24.7±12.1	336.9±249	6.5±9.5	270.6±165.9	205.9±314.7
Normal controls (60)	36±15	12.6±2.1	86.7±4.5	95.8±40.0	282.9±56.5	51.0±63.3	287.5±130.4	61.3±17.4

**Mean±SD; MCV: mean corpuscular volume; TIBC: total iron binding capacity; **H. pylori as only finding.*

and antiparietal cell antibodies, 5 were already on B_{12} treatment at the time of referral, and an additional 17 had subnormal (39-181 pg/mL) serum B_{12} levels. *H. pylori* infection, documented by increased IgG antibody titers and confirmed by a positive urease breath test or positive gastric biopsy was the only finding established in 29 of the 150 patients (19%). Remarkably, the *H. pylori* group included 5 of the 10 patients below the age of 16 years in the entire survey. In addition to subjects in whom H pylori was the only finding, evidence of *H. pylori* infection was very common in all diagnostic categories, occurring in 77 of the 150 patients. A history suggestive of menorrhagia in the absence of other findings (apart from *H. pylori* seropositivity in 24) was found in 37 young females. Gastrointestinal lesions that may or may not have been relevant to the causation of IDA were encountered in 26 patients. These included hiatus hernia (n=12), bleeding hemorrhoids (n=5), gastroplasty performed for morbid obesity (n=4), polyps of colon (n=2), and one each with diverticulosis, nasopharyngeal bleeding and cancer of the colon. Positive evidence of blood loss was only present in 7 of the patients with anatomic gastrointestinal lesions (overt history of bleeding in 4 and positive occult blood in 3). Eight patients were newly diagnosed with celiac disease presenting with IDA as the only clinical manifestation. No underlying disease could be established in 10 subjects, all but one of whom were females. Many of the patients had more than one abnormality that may have contributed to the development of IDA. Thus, of the 40 patients with hypergastrinemia with antiparietal antibodies, additional findings included *H. pylori* (n=15), menorrhagia (n=4), use of aspirin (n=2), gastrointestinal lesions (n=1) and in one patient celiac disease diagnosed 30 years previously but still positive for endomysial antibodies. Likewise, in addition to the 29 subjects in whom *H. pylori* was the only finding, *H. pylori* infection was also documented in most other diagnostic categories including the 15 patients with hypergastrinemia and APCA mentioned above, 24 with menorrhagia, 10 with gastrointestinal lesions and one with celiac disease. Menorrhagia, listed as the main diagnosis in 37 subjects was also present in 8 with hypergastrinemia and APCA and in 1 with celiac disease.

Concurrent use of aspirin was recorded in 9 patients and of rofecoxib (an NSAID) in one. The mean age of these patients was 60±16 years. Six of these patients belonged to the group with anatomical evidence of gastrointestinal lesions and of the others, 2 had hypergastrinemia with positive APCA and 2 were *H. pylori*-positive.

Laboratory findings

Pertinent laboratory findings in the various diagnostic categories are shown in Table 1. The table also lists findings in 60 asymptomatic controls of comparable age and gender (9 males and 51 females) without anemia, referred for evaluation of minor abnormalities such as suspected thrombophilia, no disease or borderline white blood cell counts. None of the 60 non-anemic controls had positive serology for antiendomysial antibodies. In 2 of the 60 antiparietal cell antibodies were weakly positive (1+) but without hypergastrinemia. *H. pylori* seropositivity was equally common among controls (31 of 60 or 51.7%) and IDA patients (77 of 150 or 51.3%). While mean hemoglobin, MCV, serum iron and serum ferritin

were significantly lower and total iron binding capacity significantly higher in IDA than in controls ($p<0.0001$), there was remarkably little inter-group variation among the various subgroups of IDA except for age which was significantly higher in patients with gastrointestinal lesions (59±19 years) than in all other groups ($p<0.001$). Serum gastrin in the hypergastrinemia group was 9-fold higher than in the controls (552±450 *vs* 61±17 pg/mL; $p<0.0001$). Moderately increased gastrin values in IDA patients were also encountered in association with *H. pylori* (86±57 pg/mL; $p=0.0097$) and gastrointestinal lesions (89±47 pg/mL; $p=0.0019$), but many in the latter group of patients were on concurrent H2 antagonist or proton pump inhibitor treatment which may have contributed to their moderately increased gastrin values.

There were 10 patients younger than 16 years of age. One had gross epistaxis and is listed under gastrointestinal lesions. Of the remaining 9, 5 had *H. pylori* as the only diagnosis and 4 had hypergastrinemia with APCA of whom 3 had coexistent *H. pylori*. Of the 8 children with *H. pylori,* with or without hypergastrinemia and APCA, 6 had gastric biopsies. These showed antral gastritis and follicular gastritis in 5, and atrophic gastritis in 1. *H. pylori* infection was diagnosed by biopsy (histology and rapid staining CLO test) in 4, and by the urease breath test in 4.

Response to oral iron treatment

Of all 150 patients, 82 (63%) were refractory to oral iron treatment and 48 had an increase of more than 1.0 g/dL hemoglobin in 2 months. In the remaining 20 patients, response was not evaluable because of intolerance to oral iron (n=4), non-compliance including failure to attend follow-up (n=10), or the patients' decision to prefer upfront parenteral iron treatment (ferric sucrose, Venofer) (n=3). Two patients received iron and triple therapy simultaneously and one required blood transfusion because of active gastrointestinal bleeding. All 8 patients (100%) with celiac disease and the 4 with gastroplasty (listed under *gastrointestinal lesions*) were refractory to oral iron treatment. The rate of refractoriness to oral iron treatment in the other diagnostic groups listed in decreasing order of magnitude was: hypergastrinemia with antiparietal antibodies 24 of 34 (71%); *H. pylori* without other findings 15 of 22 (68%); gastrointestinal disease excluding gastroplasty 6 of 16 (38%); menorrhagia without other findings 5 of 13 (38%); and negative work-up, 1 of 9 (11%).

Hypergastrinemia with antiparietal antibodies

This combination of findings, encountered in 40 of the 150 patients (27%), is described in detail in Table 2. The mean age of these patients was 39±17 years and all but 6 were females. They all had moderate to severe IDA as judged by their hemoglobin, MCV, and ferritin measurements. Many of them had evidence supporting a high likelihood of increased blood loss including 8 with a history of menorrhagia, 4 with positive occult blood tests, and 3 with bleeding gastrointestinal lesions including colon cancer, gastric polyps and gastric erosions. Two patients were referred with anemia of pregnancy and one was known to have celiac disease. Altogether, 18 of these patients had common and well established causes of IDA and in the rest, the very high proportion of young females indicated an increased likelihood of menstrual blood loss as the underlying cause of IDA.

Reports of histologic studies of the gastric mucosa were available for 20 patients. These showed chronic gastritis or atrophic gastritis (n=7), antral gastritis or follicular gastritis (n=4), apparently normal mucosa (n=6), gastric polyp (n=1), celiac disease documented by duodenal biopsy and serology (n=1) and deformed duodenum (n=1). Anti-intrinsic factor antibodies were tested in 16 patients and were positive (> 1.0) in 8 (50%). Thyroid disease (myxedema in 3 and thyrotoxicosis in 2 patients) was quite common. Of the 40 patients with IDA associated with hypergastrinemia and antiparietal antibodies, 5 were already on B_{12} replacement therapy at the time of presentation and another 14 had low serum B_{12} values ranging from 39 to 181 pg/mL. Three additional patients with normal initial serum B_{12} developed low B_{12} levels within one to two years of follow-up.

Evidence of coexistent active *H. pylori* infection was found in 15 patients, with positive *H. pylori* serology confirmed by positive urease breath test or gastric biopsy. In nine of these, *H. pylori* was eradicated by triple therapy, as described in the following section. Successful *H. pylori* eradication was indicated by a negative repeat urease breath test and a slow but steady decline in *H. pylori* antibody titers. Although this was followed by decreased serum gastrin levels in most cases, as shown later, in none of the patients did we observe the disappearance of serum antiparietal antibodies. Moreover, the first of our patients described in the next section as IDA associated with *H. pylori* gastritis diagnosed at the age of 14 years old and cured of refractory IDA by triple therapy, developed after 3 years of follow-up hypergastrinemia, positive APCA, positive anti-intrinsic factor antibodies, and low serum B_{12} consistent with autoimmune atrophic gastritis, and is presently on B_{12} eplacement therapy.

H. pylori infection

In order to examine the possible effect of *H. pylori* seropositivity on iron status in normal subjects, serum iron, TIBC, ferritin and serum gastrin were compared within the subgroups of *H. pylori* seroneg-

Table 2. IDA patients with hypergastrinemia and parietal cell antibodies.

Age yrs.	*Sex*	*Hemoglobin g/dL*	*MCV fL*	*Ferritin µg/L*	*B_{12} pg/mL*	*Gastrin pg/mL*	*APCA*	*Anti IF IU*	*Gastric mucosa*	*Additional findings*
44	F	9.8	74	6	237	339	3+	0.1	Atrophic gastritis	
40	F	9.3	81	3	153	734	3+			
37	F	9.2	66	3	570 Tx	856	3+		Normal	
47	F	10.5	76	3	242	371	2+			
34	F	8	67	2	238	185	3+	1.7	Atrophic gastritis	Myxedema
28	F	8.2	67	6	100 >	338	1+	0.1		Thyrotoxicosis
47	F	8.8	65	3	141	580	2+			
57	F	10	76	6	366	1088	4+	1.3	Atrophic gastritis	
76	F	10.2	90	8	127	187	3+	1.2		DM
68	F	9.6	79	21	230	1464	4+		Atrophic gastritis	DM
72	F	9.8	82	4	323	125	3+	0.7	Normal	DM, thyrotoxicosis
9	F	10.2	60	3	460	799	4+	4	Chronic folliular gastritis	Occult blood +
39	F	10	82	3	155	904	4+	0.3	Thick antral mucosa	Occult blood +
48	F	8.5	55	4	211	567	3+	0.7		Menorrhagia
24	F	7.9	62	1	202	610	3+			Menorrhagia, myxedema
28	F	9.4	68	3	138	1312	3+			Menorrhagia
42	F	9.3	82	3	94 Tx	251	3+		Atrophic gastritis	Menorrhagia
34	F	9.3	67	2	180	472	3+			Menorrhagia
18	F	8.3	69	1	225	246	4+			Menorrhagia
31	F	8.3	69	7	175 Tx	961	3+	0.1		Menorrhagia, myxedema
41	F	9.1	62	3	142	63	2+			Pregnancy
53	M	8.8	50	1	186	676	2+		Gastric polyp	Thal minor
77	M	6.8	73	18	186	1112	3+	0.8	Deformed duodenum	Ca colon
47	F	7.9	66	2	237	327	3+			Celiac disease
57	F	7.7	60	2	167	80	3+		Chronic gastritis, erosions	Hiatus hernia
29	F	7.5	80	6	39	83	4+			HP, pregnancy
41	F	10.9	69	6	1000 Tx	289				HP
19	F	10.8	76	3	225	482	4+			HP
42	M	11.2	78	9	181	556	3+		Normal	HP
41	F	8.1	68	5	207	1459	4+	0.1	Chronic gastritis	HP
31	M	9.3	62	8	200	421	4+	5.4	Normal	HP
47	F	9.4	76	3	236	536	3+	5.6		HP
13	M	11.9	78	6	546	108	4+			HP
12	F	9.7	69	1	343	199	3+			HP
45	F	8.7	77	30	155	173	3+	1.7		HP, menorrhagia
38	F	10.5	76	5	142	585	3+		Antral gastritis	HP
42	F	9.7	70	2	150	2000	4+		Normal	HP
29	F	10.3	69	5	284 Tx	158	3+			HP
18	M	10.7	75	6	234	205	4+	3.1	Normal	HP, occult blood +
11	F	9.2	62	2	727	160	4+		Mild antral gastritis	HP, occult blood +

MCV: mean corpuscular volume; APCA: antiparietal cell antibodies; Tx: on concurrent B12 treatment; DM: diabetes mellitus; HP: Helicobacter pylori; IF: intrinsic factor.

ative (n=29) and seropositive (n=31) controls. There was no significant difference in parameters reflecting iron status between the two groups, although serum iron (92±37 vs 102±44; p=0.6) and serum ferritin (42±35 vs 60±87; p=0.17) were slightly lower in *H. pylori*-positive subjects. Conversely, serum gastrin values were slightly but significantly higher (67±18 *vs* 57±12, p= 0.016) in *H. pylori* seropositive subjects.

In the next phase of our study, we examined the effect of *H. pylori* infection and its subsequent eradication on response to oral iron therapy. Information on response to oral iron treatment prior to *H. pylori* eradication was available for 77 patients (Table 3). This analysis excluded subjects with hypergastrinemia with APCA, celiac disease, and gastroplasty as in these conditions the underlying disease was already believed to preclude a normal response. Both the *H. pylori*-negative, and positive groups consisted of three categories: patients with no underlying disease, menorrhagia, or gastrointestinal lesions. Of these, 29 were *H. pylori*-negative, and 48 *H. pylori*-positive (serology confirmed by urease breath test). Of the 29 *H. pylori*-negative patients, 21 (72%) responded to oral iron treatment and 8 (28%) were refractory. By contrast, of the 48 *H. pylori*-positive patients, 15 (31%) were responsive and 33 (69%) were refractory. Thus, failure to respond to oral iron treatment in *H. pylori*-positive patients was more than twice as common as in the *H. pylori*-negative group (χ^2 square p=0.007).

Table 3. Effect of *H. pylori* status on response to oral iron treatment prior to triple therapy.

Condition	*Responsive*	*Refractory*	*Total*
Negative	8	1	9
Menorrhagia	8	5	13
Gastrointestinal	5	2	7
All Hp negative	21 (72%)	8 (28%)	29 (100%)
Negative + Hp*	7	15	22
Menorrhagia +Hp	3	14	17
Gastrointestinal +Hp	5	4	9
All Hp positive	15 (31%)	33 (69%)	48 (100%)

**Hp: H. pylori; χ^2 p=0.007.*

Response to triple therapy

Of the 77 patients in whom *H. pylori* seropositivity was confirmed by the urease breath test, 22 were not treated because failure to attend follow-up (n=10), improvement of anemia on iron alone (n=5) or advanced pregnancy managed by intravenous iron (n=7). Of the 55 subjects who received triple therapy, 15 failed to complete the follow-up and 40 had a complete evaluation including repeat urease breath test one month after treatment. In all patients, *H. pylori* eradication was documented by conversion of a positive urease breath test to a negative one month or more after treatment, and monitored by subsequent changes in hemoglobin, serum gastrin and *H. pylori* antibody titers. All patients were maintained on the same oral iron treatment before and after triple therapy. Successful eradication was achieved in 29 (73%) of the 40 patients. The effect of *H. pylori* eradication is illustrated in Figures 1 A-C. *H. pylori* eradication was followed by an increase in hemoglobin from 9.7±1.3 (mean±SD) before, to 13.2±1.4 within 3 to 6 months after eradication (p<0.001 by the paired t test). Simultaneously, *H. pylori* eradication was followed by a decrease in serum gastrin from 233±296 to 94±75 (p=0.04) and a decrease in *H. pylori* IgG antibody titer from 4.58±2.19 to 1.78±0.87 (p=0.02).

Finally, the effect of *H. pylori* eradication and continued iron treatment was examined in the subgroup of 26 evaluable patients who were refractory to oral iron treatment prior to triple therapy (Figures 2 A-B). Successful *H. pylori* eradication and continued oral iron treatment in 19 previously refractory patients resulted in an increase in hemoglobin from 9.4±1.5 (mean±SD) before, to 13.5±1.2 within 3 to 6 months after eradication (p<0.001 by the paired t test). By contrast, in the 7 patients failing *H. pylori* eradication, the increase in hemoglobin following antibiotic treatment was less than 1 g/dL, from 9.2±1.1 (mean±1SD) before, to 9.8±1.2 after treatment (NS, p=0.2).

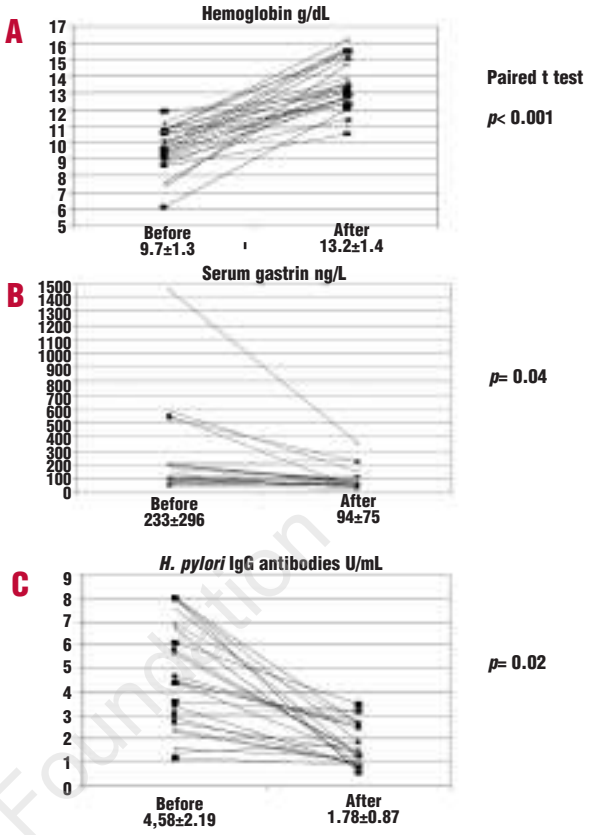

Figure 1. Effect of *H. pylori* eradication on anemia (A), serum gastrin (B) and *H. pylori* antibodies (C). Paired values for individual patients on continued oral iron treatment before, and after (3 to 6 months) eradication of *H. pylori*, documented by negative urease breath test.

Discussion

Patients with unexplained or refractory IDA are often referred for hematologic evaluation when the likelihood of gastrointestinal pathology is *a priori* low, such as in fertile females, or subjects in whom a routine gastrointestinal work-up failed to document a source of blood loss. Based on current literature, we anticipated that a certain proportion of our patients would have celiac disease with IDA as the only apparent clinical manifestation.[4-10] Indeed, 5% of our patients have been diagnosed *de novo* as having celiac disease identified first by serological tests and subsequently confirmed by duodenal biopsy and a satisfactory response to a gluten-free diet. Excessive menstrual blood loss and low compliance with iron therapy are important factors in the causation and per-

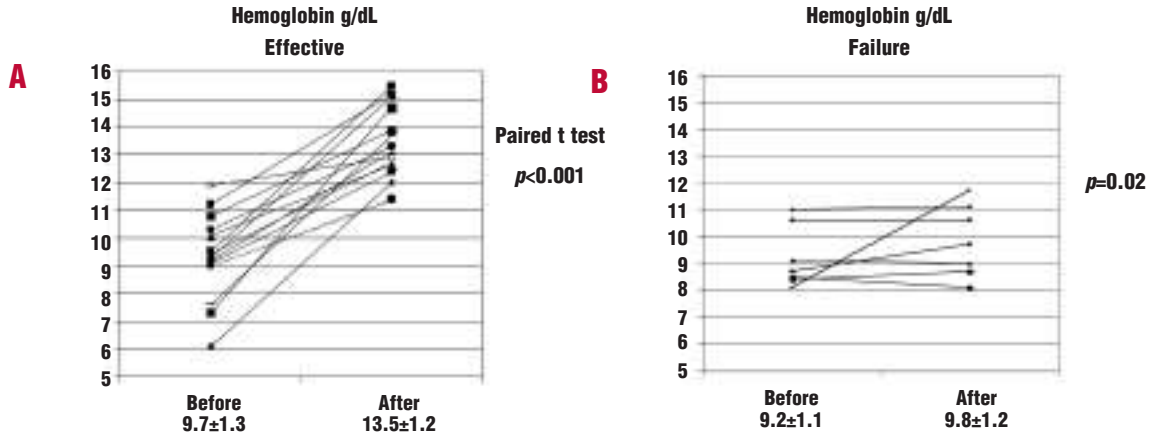

Figure 2. Effect of *H. pylori* eradication on anemia in patients previously refractory to oral iron treatment. Paired values for individual patients before and after (3 months or more) triple therapy and continued oral iron treatment. A. Effective eradication of *H. pylori* documented by a negative urease breath test. B. Failure of eradication documented by continuously positive urease breath tests.

petuation of unexplained or refractory anemia in fertile women. The prevalence of IDA in fertile women is about 10 times higher than in men of comparable age[1] and this is largely attributed to increased menstrual blood loss even if this cannot be established by a careful menstrual history. Indeed, the vast majority of the present series and all but one of the 10 patients with no underlying disease demonstrated were women of reproductive age with no clinical evidence of gastrointestinal blood loss. Low compliance in some of these patients is reflected in the proportion of subjects failing to return for the follow-up visits required to evaluate their response to treatment.

Nevertheless, the present findings provide strong evidence supporting the role of the gastric mucosa in unexplained or refractory IDA in two clinical entities which are not yet widely recognized as common causes of IDA: *autoimmune atrophic gastritis* manifested by hypergastrinemia in combination with antiparietal antibodies (APCA) and *H. pylori gastritis*, with considerable overlap between these two conditions.

Autoimmune atrophic gastritis, manifested by hypergastrinemia with strongly positive APCA, was encountered in 40 (27%) of our 150 subjects with IDA. These patients were much younger than patients with classical pernicious anemia presenting with macrocytic anemia and, unlike pernicious anemia in the elderly, in which males and females are similarly affected[27] all but 6 of our 40 patients were females. Abnormal gastric mucosa including atrophic gastritis, chronic gastritis, antral or follicular gastritis was present in 14 of the 20 patients for whom information on this was available. The apparently normal appearance of gastric mucosa in 6 of our patients is probably explained by the lack of multiple mucosal biopsies in these subjects. The close relation of this condition to pernicious anemia is further indicated by the high prevalence of thyroid disease and the observation that 22 (55%) of our patients had low concentrations (39-181 pg/mL) of serum B_{12} or were already on cobalamin treatment at presentation, or developed low serum B_{12} during the follow-up. Finally, the finding of increased intrinsic factor antibody titers in 50% of the 16 subjects tested confirms a high degree of overlap between hypergastrinemia and APCA presenting as IDA and classical pernicious anemia.

The concept of gastric atrophy as a cause of iron deficiency anemia is not new. *Achylia gastrica* associated with iron deficiency anemia was described as a clinical entity by Faber as early as 1909[21] and *achlorhydric gastric atrophy*, a synonym for the same entity, has long been recognized as a major cause of iron deficiency anemia[22,23,28] but largely forgotten, and completely ignored in subsequent major surveys of gastrointestinal causes of iron deficiency anemia.[2,3] More recently, achlorhydric gastric atrophy was rediscovered by Dickey *et al.*,[18] and information on this condition greatly extended in a series of important studies by Annibale *et al.*[19,20] Iron absorption is heavily dependent on normal gastric secretion for solubilizing and reducing dietary iron and is impaired by the achlorhydria associated with atrophic gastritis.[29-31] Age, gender, and severity of disease may be critical in determining whether the clinical presentation is in the form of microcytic iron deficiency anemia or macrocytic megaloblastic anemia. Although atrophic gastritis may impair both B_{12} and iron absorption simultaneously, in young women in whom menstruation represents an added strain on iron requirements, iron deficiency will develop many

years before the depletion of B_{12} stores. *Helicobacter pylori*. The role of *H. pylori* in the causation of IDA is at present unsettled as *H. pylori* infection is very common in the normal population[32] Major population surveys involving thousands of subjects[33-36] conducted over diverse geographic areas all indicate that *H. pylori* positivity is associated with a slight and significant decrease in serum ferritin levels implying diminished iron stores, but there was no evidence of a high prevalence of iron deficiency anemia associated with *H. pylori* seropositivity in the populations at large. Nevertheless, in a subset of patients, a cause-and-effect relation between *H. pylori* and serious gastrointestinal pathology including duodenal ulcer, atrophy of the gastric body predisposing to gastric ulcer and cancer, and the formation of mucosa-associated lymphoid tissue (MALT) lymphoma has been established and strongly supported by the beneficial effect of H pylori eradication in these conditions.[37] Consequently, if evidence is sought for a cause-and-effect relation between *H. pylori* and IDA, it could be more rewarding to focus on the functional effects of *H. pylori* eradication on refractory IDA than to study large numbers of unselected and apparently healthy individuals.

Because refractoriness to oral iron treatment was very common, we first examined the effect of *H. pylori* status on response to oral iron treatment prior to triple therapy. Patients with menorrhagia, gastrointestinal lesions or no abnormal findings were compared with the same diagnostic categories who in addition were also *H. pylori* positive. All patients with hypergastrinemia and antiparietal antibodies were excluded from this comparison because in advanced gastric mucosal atrophy. *H. pylori* infection is spontaneously eliminated[38] due to the unfavorable effect of achlorhydria on the growth and colonization of this pathogen. Our observation that failure to respond to oral iron treatment was more than twice as common in *H. pylori* positive patients than in the *H. pylori* negative group suggests that *H. pylori* infection has an unfavorable effect on response to oral iron treatment in IDA.

In view of these considerations, it was reasonable to ask whether eradication of *H. pylori* would be followed by improved response to oral iron in previously refractory patients. Indeed, successful *H. pylori* eradication resulted not only in a significant post-treatment decrease of serum gastrin and *H. pylori* IgG antibody titers, but an increase in hemoglobin levels indistinguishable from that in previously responsive IDA patients. Conversely, in patients in whom *H. pylori* eradication failed, the increment in hemoglobin despite continued oral iron treatment was insignificant. Our findings indicate that whether encountered alone or in combination with other, established causes of IDA, *H. pylori* infection may be a cause of refractoriness to oral iron treatment with improved response to oral iron following its eradication. Our observations are in agreement with a number of previous studies on the effect of *H. pylori* eradication on IDA in patients in whom no other cause of anemia could be identified.[12-17,39,40]

A number of possible mechanisms have been invoked to explain the relation between *H. pylori* gastritis and IDA including occult gastrointestinal bleeding[41] and competition for dietary iron by the bacteria.[42] However, the most likely explanation is the effect of *H. pylori* on the composition of gastric juice.[45-47] Studies by Annibale and others[44] have shown that gastric acidity and ascorbate content, both of which are critical for normal iron absorption,[29,48,49] are adversely effected by *H. pylori* infection and, that *H. pylori* eradication results in normalization of intragastric pH and ascorbate content. The possibility that *H. pylori* may also play a role in the pathogenesis of autoimmune type A atrophic gastritis and pernicious anemia[20,50-52] is intriguing, but outside the scope of the present study. Although in our patients with autoimmune gastritis and coexistent H pylori infection, successful *H. pylori* eradication was followed by decreased serum gastrin levels in most cases, in none of these patients did we observe the complete disappearance of antiparietal antibodies.

In view of the data presented here, there are two categories of patients in whom simple non-invasive screening may be recommended: (a) males and postmenopausal females with IDA in whom no cause has been identified by endoscopic and radiological studies, representing 36 to 38% of subjects, and (b) fertile females and children/adolescents who are refractory to oral iron treatment. In such patients a rapid screening for celiac disease (anti-endomysial antibodies) autoimmune type A atrophic gastritis (gastrin, antiparietal antibodies) and *H. pylori* (IgG antibodies followed by a urease breath test) may provide a high-sensitivity screening and an effective starting point for further investigations. The implications of diagnosing celiac disease or autoimmune atrophic gastritis for abnormal iron absorption are obvious. Interpretation of positive serology for *H. pylori* confirmed by a positive urease breath test requires clinical judgment as 20 to 50% of the general and largely healthy population in industrialized countries will have such findings. In such patients, refractoriness to oral iron treatment may justify a *test-and-treat* approach of *H. pylori* eradication as currently advocated for the management of dyspeptic patients.[54-59] Cure of previously refractory IDA by *H. pylori* eradication could then be regarded as evidence supporting a cause-and-effect relation between *H. pylori* and refractory IDA.

Capsule endoscopy is an innovative technology for the documentation of obscure gastrointestinal blood loss undiagnosed by conventional endoscopy. It is highly effective in patients with active bleeding and IDA patients with guaiac-positive stools. However its efficacy in the absence of such findings is limited[60] and it is not recommended for a young female population with no evidence of gastrointestinal blood loss.

Renewed awareness of the critical importance of gastric secretion for iron absorption, and the recognition that chronic iron malabsorption may be a significant factor contributing to the development of unexplained, or refractory IDA in a high proportion of patients, should have a strong impact on the daily practice of diagnosing and managing IDA. Optimally, this should involve a multidisciplinary approach with close collaboration of hematologists and gastroenterologists. Because abnormal gastric secretion is the common underlying abnormality responsible for poor iron absorption in both *H. pylori* gastritis and autoimmune type A atrophic gastritis, and because these two entities often overlap and may represent the two ends of the same spectrum, the term *gastropathic sideropenia* may be appropriate for underlining the role of abnormal gastric mucosa in the pathogenesis of IDA.

CH, MS, IM: clinical and laboratory workup for hematological evaluation; DK: gastroenterological evaluation; YM: immunological evaluation; AL: statistical analysis; VH: critical analysis and reorganization of data, and active participation in preparation of the manuscript. CH was personally responsible for the conception of the study, clinical care of all patients, data collection, interpretation of results and preparation of the manuscript. The authors declare that they have no potential conflict of interest.

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