

Atrophic Body Gastritis in Patients With Autoimmune Thyroid Disease

An Underdiagnosed Association

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Background: Atrophic body gastritis (ABG) has never been histologically characterized in patients with autoimmune thyroid disease (AITD), and its prevalence may be substantially different from that previously assessed based on only indirect evidence.

Objective: To detect and characterize the presence of ABG in patients with AITD.

Methods: Sixty-two patients with AITD (5 men and 57 women), aged between 21 and 74 years, have been screened for the presence of ABG by assaying serum gastrin levels. Patients with hypergastrinemia underwent gastroscopy followed by the histological examination of multiple biopsy specimens. The diagnosis of ABG was based on hypergastrinemia and pentagastrin-resistant achlorhydria, confirmed by histological examination.

Results: Twenty-two (35%) of 62 patients had hypergastrinemia (mean \pm SEM gastrin level, 1070 \pm 288

pmol/L). The diagnosis of ABG has been histologically confirmed in all 22 patients, and the score of atrophy was moderate to severe. In group A (patients aged 20-40 years; n = 21), 6 patients (29%) had ABG, compared with 11 patients (37%) in group B (patients aged 41-60 years; n = 30) and 5 patients (45%) in group C (patients aged 61-80 years; n = 11). Antiparietal cell antibodies were detected in only 68% (15/22) of patients with ABG. Anemia was observed in 82% (18/22) of patients with AITD and ABG but only in 22% (9/40) of patients without ABG ($P < .0001$).

Conclusions: In the patients with AITD studied, about one third had ABG, which was diagnosed also in young patients; the measurement of gastrin levels represented the most reliable tool in the diagnosis of ABG; and the presence of anemia, even microcytic, was suggestive of undiagnosed ABG.

Arch Intern Med. 1999;159:1726-1730

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THE ASSOCIATION between autoimmune thyroid disease (AITD) and various other autoimmune diseases was first suggested in the early 1960s.¹⁻⁴ Indeed, the term thyrogastric autoimmunity or disease has been used to define the prevalence of thyroid autoantibodies^{3,5-7} and/or overt AITD in patients with pernicious anemia (PA),⁸ which, in turn, was improperly used as synonymous with atrophic gastritis.⁹ More recently, the association between AITD and PA has been included in type IIIb polyglandular autoimmune disease.¹⁰ However, atrophic gastritis is represented by more than one distinct pathophysiological and clinical entity, which may precede the onset of PA by several years.^{9,11,12} In particular, atrophic body gastritis (ABG), formerly known as type A, represents a chronic, symptomless gastritis of the fundic mucosa, which often has an autoimmune pathogenesis,¹² is involved in

gastric carcinogenesis,¹³ and is closely related to the appearance of microcytic anemia^{4,14} and PA.^{8,9} To our knowledge, ABG has not yet been directly characterized in patients with AITD, and its prevalence may be substantially different from that previously assessed only by indirect evidence (ie, the presence of antiparietal cell antibodies [APCAB] and/or PA).^{3,5-8,15} Furthermore, the prevalence of AITD, namely, lymphocytic thyroiditis, in its subclinical form appears to have increased during the past 10 years, probably because of the availability of more sensitive diagnostic tools.^{16,17}

This study, therefore, aimed to detect and characterize the presence of histologically and functionally proved ABG in patients with AITD.

RESULTS

Plasma gastrin levels were increased in 22 (35%) of 62 patients (median, 577 pmol/L;

PATIENTS AND METHODS

For 13 months, 1035 outpatients were sequentially examined by the same physician (M.C.) in our tertiary outpatient Center for Thyroid Disease, University of Rome "La Sapienza," Rome, Italy. Autoimmune thyroid disease was diagnosed in 62 patients (6.0%) (5 men and 57 women) aged 21 to 74 years (mean \pm SD, 47.5 \pm 14.0 years), who, besides other criteria, displayed pathological levels of antiperoxidase antibodies (>200 U/L; median, 1380 U/L; range, 269-6500 U/L) at the time of diagnosis and in at least 2 measurements during a 12-month period. This cohort represented the study population. At presentation, 26 patients were clinically euthyroid, 26 had overt or subclinical hypothyroidism, and 10 had hyperthyroidism. Patients were divided according to age as follows: group A, 20 to 40 years ($n = 21$); group B, 41 to 60 years ($n = 30$); and group C, 61 to 80 years ($n = 11$). Chronic autoimmune thyroiditis was diagnosed in 52 patients, 47 with goiter (Hashimoto thyroiditis) and 5 without goiter (atrophic thyroiditis). Graves disease was diagnosed in 10 patients. Serum gastrin levels and the presence of APCAb and *Helicobacter pylori* IgG antibodies, as well as that of anemia, were evaluated in all patients. Patients with increased fasting gastrin levels, which represent a regular feature of gastric atrophy,¹⁸⁻²⁰ underwent further functional and morphologic characterization of the fundic mucosa of the stomach by gastric secretory tests, gastroscopy, and histological evaluation of multiple biopsy specimens, which were obtained during the gastroscopic examination. However, a higher gastrin level cutoff (>210 pmol/L; 2.5 times the cutoff of the method) was used in this study, as a small increase of the gastrin levels, due to *H pylori* infection and not related to gastric atrophy, has been reported.²¹ This clear-cut criterion has been used to avoid gastroscopic examinations,

which, in patients without definite clinical and/or biochemical evidence of gastric atrophy, would not have been strictly necessary. However, patients without hypergastrinemia (gastrin level >210 pmol/L) but showing the presence of APCAb also underwent gastroscopy and histological evaluation of multiple biopsy specimens to compare the reliability of this diagnostic parameter as a marker of ABG.^{3,6,12}

Informed consent was obtained from each patient before any invasive procedure, and the protocol was consistent with the Declaration of Helsinki.

DIAGNOSIS OF AITD

Diagnostic procedures included routine clinical examinations, serum free triiodothyronine and free thyroxine and basal thyrotropin measurements, antiperoxidase antibody detection, and ultrasonography. Where appropriate, patients underwent radioiodine uptake and scintigraphic mapping, ultrasonography-assisted fine needle aspiration biopsy, and a thyrotropin-releasing hormone test for serial thyrotropin measurements and detection of anti-thyrotropin receptor antibodies in serum. The antiperoxidase and anti-thyrotropin receptor antibodies were measured by a radioligand assay (intra-assay variation, 3.6%; interassay variation, 4.6%) (Radim Techland, Liege, Belgium) and a radioreceptor assay (Ares-Serono, Milan, Italy), respectively. Free triiodothyronine and free thyroxine levels were assayed by radioimmunoassay (Ares-Serono). Thyrotropin levels were assayed by immunoradiometric assay (Radim Techland).

DIAGNOSIS OF ABG

The diagnosis of ABG was based on hypergastrinemia and pentagastrin-resistant achlorhydria, confirmed by

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range, 231-5250 pmol/L). In these patients, the mean gastrin levels were more than 10 times higher than the upper reference value, and basal and stimulated acid secretion were practically absent (**Table 1**). The results of the gastroscopic examination, with histological evaluation of the biopsy tissue, confirmed the presence of ABG in all 22 patients (19 women and 3 men) with hypergastrinemia, and their mean score of gastric injury ranged from mild to moderate (Table 1). The mean levels of gastrin, peak-stimulated acid output, and basal acid output and the score of gastritis, according to the Sydney score,²⁵ of patients with ABG are summarized in Table 1. The prevalence of *H pylori* infection was not different in patients with or without ABG, as analyzed by the Fisher test (54% vs 46%, $P = .42$). As expected, an apparently higher prevalence of ABG (5 [45%] of 11) was found in the older patients (group C) (**Figure 1**). However, it was also detected in several middle-aged patients (group B) (11 [37%] of 30) and even in young patients with AITD (group A) (6 [29%] of 21) (Figure 1); moreover, the different prevalence of ABG between the groups was not statistically significant, as ascertained by the Fisher test. The analysis of thyroid homeostasis revealed that 10 of 22 patients with ABG were euthyroid, 10 were hypothyroid, and 2 were hyperthyroid. Most cases of ABG were associated with

Hashimoto thyroiditis; the remaining cases were associated with atrophic thyroiditis or Graves disease. There was no relationship between the clinical diagnosis of thyroid disease and the presence of ABG (**Table 2**).

The occurrence of anemia has been reported in patients with AITD and in patients with ABG.^{7-12,14,26} Although these reports mainly dealt with PA, the presence of an iron-deficient microcytic anemia has also been described in patients with AITD²⁷ and even in patients with ABG,^{4,14} the latter finding being in keeping with a hypochlorhydria-related iron deficiency.²⁸ Screening for the presence of anemia was, therefore, carried out in all patients and, indeed, was detected in 27 (43%) of 62 patients (**Table 3**). Morphologic analyses revealed that anemia was microcytic in 15 patients and macrocytic in 12. In 10 of these 12 patients, the macrocytic anemia met the criteria of PA; all of these patients belonged to the group with ABG. As expected, the prevalence of microcytic anemia decreased whereas that of macrocytic PA increased with increasing age of patients (data not shown). Anemia was present in 18 (82%) of 22 patients with ABG, and in only 9 (22%) of 40 patients without ABG. The Fisher exact test revealed a significant difference between the 2 subgroups ($P < .0001$; 95% confidence interval, 4.2-57.6) (Table 3).

histological examination of multiple specimens obtained at gastroscopy, as previously reported.²² The endoscopist was unaware of the clinical data of the patients. Fasting plasma gastrin levels were evaluated by a specific radioimmunoassay using antibody 4562, as previously described.²³ The reference level in our laboratory is 80.2 pmol/L.²⁴ Serum APCAb were determined using a solid-phase immunosorbent assay commercial kit (Autostat; Cogent Diagnostics, Ltd, Edinburgh, Scotland) with a variation coefficient of 14.3%, as previously described.²¹ *Helicobacter pylori* status has been routinely assessed by serologic examination and, in patients who underwent endoscopy, also by histological evaluation. *Helicobacter pylori* IgG antibodies were detected by an enzyme-linked immunosorbent assay commercial kit (GAP test IgG; Biorad, Milan). Basal acid output and peak-stimulated acid output (using pentagastrin, 6 µg, subcutaneously) (Peptavlon, Zeneca, England) were determined in all patients with hypergastrinemia as described elsewhere.²³ The reference values in our laboratory are as follows: median, 4.1 mEq/h (range, 1.2-11.2 mEq/h) for basal acid output; and median, 31.1 mEq/h (range, 13.0-44.4 mEq/h) for peak-stimulated acid output.²⁴

HISTOLOGICAL PROCEDURES

Four biopsy specimens were obtained from the midbody mucosa, along the greater curve of the stomach.²² Specimens were immediately fixed in Bouin solution for 4 to 8 hours at room temperature, rinsed in 0.1% phosphate-buffered saline, pH 7.4, and routinely processed to wax. Serial paraffin sections (5 µm) were stained with hematoxylin-eosin for conventional histological examination by the same histopathologist, who was unaware of the clinical data of the patients. Atrophy of the fundic mucosa was defined as focal or complete loss of oxyntic glands and/or

replacement by metaplastic pyloric or intestinal glands.²² The degree of gastritis was assessed according to the Sydney system and its relative score.²⁵

DIAGNOSIS OF ANEMIA

The diagnosis of microcytic anemia was based on the simultaneous presence of decreased hemoglobin level (<120 g/L for women and <136 g/L for men) and mean corpuscular volume (<80 fL), which were associated with reduced levels of serum iron (<11 µmol/L [<61 µg/dL]) and ferritin (<30 µg/L). All patients with microcytic anemia were assessed for other causes of iron deficiency, and obvious causes of blood loss (eg, overt gastrointestinal tract bleeding or excessive menstrual blood loss) were carefully checked. Furthermore, all patients were examined for occult causes of lower gastrointestinal tract bleeding: the fecal occult blood test was performed in patients 40 years and younger; and a double-contrast barium enema was given or a colonoscopy was performed, where appropriate, in those older than 40 years.

The diagnosis of macrocytic anemia was based on decreased hemoglobin levels and a mean corpuscular volume greater than 100 fL. The diagnosis of PA was based on the following criteria: the presence of macrocytic anemia, the presence of anti-intrinsic factor antibodies, pentagastrin-resistant achlorhydria, and response to cyanocobalamin therapy, as described.^{9,23}

STATISTICAL ANALYSIS

Data are expressed as the mean \pm SEM or median, where appropriate. Subgroup percentages were compared using the Fisher exact test. Software (INSTAT Graphpad [1990-92], San Diego, Calif) for DOS was used in the statistical analysis.

The reliability of the biological parameters used as diagnostic criteria of ABG in patients with AITD is shown in **Figure 2**. In the study population, the presence of APCAb was detected in 25 (40%) of the 62 patients (median, 500 U/mL; range, 130-1000 U/mL); however, APCAb were present only in 15 (68%) of 22 patients with the AITD plus ABG association. Gastroscopy was also performed in the remaining 10 APCAb-positive patients, as their presence was considered a marker of ABG^{3,6,12}; none of these patients showed histological evidence of this disease. Thus, 7 false-negative results and 10 false-positive results were due to that marker in the diagnosis of ABG. The presence of PA was diagnosed in 10 (16%) of 62 patients with AITD, all of whom had ABG. Specificity was thus 100%, but sensitivity as a marker of ABG was low (10 [45%] of 22 patients). Gastrin levels were, on the other hand, a reliable biological parameter in the screening of patients with ABG, the presence of which has been confirmed in all patients with hypergastrinemia, with no evidence of false positivity (100% specificity) (Figure 2). However, it was not possible to evaluate the sensitivity of gastrin levels as a marker, since, for the reasons previously described, not all the patients studied underwent gastroscopy. However, the gastrin levels were normal in the 10 APCAb-positive patients with no evidence

of ABG. Overall, only 7 of 22 patients with ABG presented simultaneously with hypergastrinemia, APCAb, and PA.

COMMENT

Atrophic body gastritis is an asymptomatic disease, and its prevalence has never been assessed in an unselected population.^{9,12} Nevertheless, it is important to make an early diagnosis because patients with ABG have a 3 times greater risk for developing gastric cancer,^{12,13} and ABG is responsible for unexplained iron-deficient anemia.^{4,14} The results of the present study reveal a high prevalence (35%) of ABG in patients with AITD. Such a prevalence is substantially higher than that previously reported based on indirect evidence (ie, the presence of APCAb and/or PA).^{4,26} In fact, a 12.3% prevalence of PA has been reported in patients with primary hypothyroidism²⁶; the same researchers,²⁶ however, reported that, when achlorhydria was used as a marker, the prevalence rose to 32%, a finding comparable with that recorded in the present study. The results of the present study revealed the presence of ABG in 6 of 21 young patients (<40 years) with AITD. Two (9.5%) of these patients also had PA. These findings are in contrast with those in the historical ar-

Table 1. Functional and Morphologic Factors of Autoimmune Thyroid Disease in 22 Patients With Atrophic Body Gastritis

Factors	Values*
Functional	
Fasting gastrin levels, pmol/L	1070 ± 288
Basal acid output, mEq/h	0.04 ± 0.03
Peak acid output, mEq/h	1.3 ± 0.7
Morphologic†	
Chronic inflammation	1.37 ± 0.11
Atrophy	2.42 ± 0.18
Intestinal metaplasia	1.15 ± 0.23

*All values are given as mean ± SEM.

†Values are given as updated Sydney scores. 1 indicates mild; 2, moderate; and 3, severe.

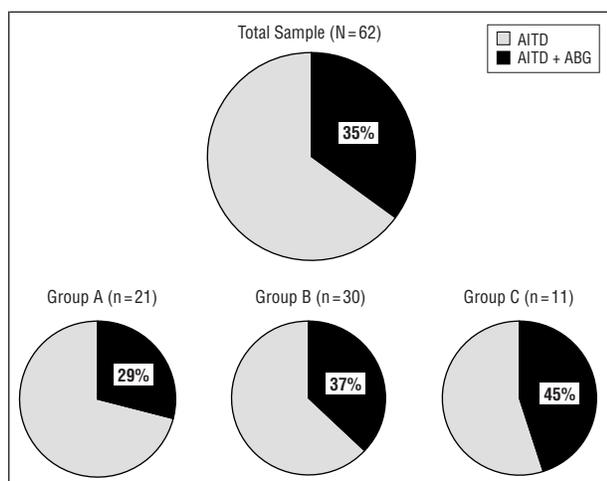


Figure 1. Prevalence of chronic atrophic body gastritis (ABG) in patients with autoimmune thyroid disease (AITD).

Table 2. Presence of Atrophic Body Gastritis (ABG) in Patients With Autoimmune Thyroid Disease (AITD) in Relation to Clinical Diagnosis

	No. (%) of Patients			P	
	Total (N = 62)	With AITD (n = 40)	With AITD and ABG (n = 22)	1*	2†
				1*	2†
Hashimoto thyroiditis	47 (76)	29 (72)	18 (82)	.77	.54
Atrophic thyroiditis	5 (8)	3 (8)	2 (9)	>.99	>.99
Graves disease	10 (16)	8 (20)	2 (9)	.72	.47

*Values derived using the total sample as a reference.

†Values derived using patients with AITD, but without ABG, as a reference.

ticle by Irvine,⁴ who reported no ABG or PA in a large cohort of patients with AITD who were younger than 40. This discrepancy could be due to the use, at that time, of less reliable markers for an early diagnosis. In fact, the detection of APCAb and the presence of PA, used at that time as markers,^{3,4,6,8} showed, in the present study, an inadequate overall accuracy in the diagnosis of this disease. The reliability of measuring fasting gastrin levels to screen patients at risk for ABG is well established^{12,15}; indeed, the most frequent cause of marked hypergas-

Table 3. Prevalence of Anemia in Patients With Autoimmune Thyroid Disease (AITD) With or Without Atrophic Body Gastritis (ABG)

Variable	No. (%) of Patients	P*	
		1†	2‡
Total	27/62 (43)
Patients with AITD and without ABG	9/40 (22)	.04	...
Patients with AITD and ABG	18/22 (82)	.002	<.0001

*Ellipses indicate data are not applicable.

†Values derived using the total sample as a reference group.

‡Values derived using patients with AITD, but without ABG, as a reference group.

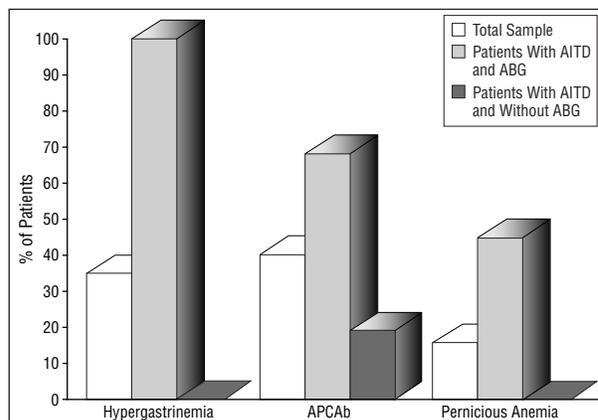


Figure 2. Reliability of different markers used in the diagnosis of atrophic body gastritis (ABG) in patients with autoimmune thyroid disease (AITD). APCAb indicates antiparietal cell antibodies.

trinemia has been shown to be represented by ABG,²⁴ although an appropriate cutoff level should be used to avoid the bias due to *H pylori* infection.²¹ The present study showed that the measurement of gastrin levels is also an important tool in the diagnostic work-up of ABG in patients with AITD, and represents a better diagnostic marker than those previously advocated.^{3,4,6,8,15}

The presence of anemia has been described in patients with impaired thyroid homeostasis,²⁷ mainly referred to as PA.^{7,8,26} The results of this study confirm the higher prevalence of anemia in patients with AITD compared with that reported in referral patients.²⁹ However, a marked difference has been found between patients with and those without ABG (82% vs 22%, $P < .001$), which was only partly due to the prevalence of PA. This fact indicates that, particularly in young patients with AITD, even the presence of unexplained microcytic anemia should be considered as highly suggestive of the presence of undiagnosed ABG. This assumption is in keeping with the finding that hypochlorhydria may lead to iron deficiency and anemia.²⁸ In this respect, all patients with AITD should be routinely monitored at follow-up for the presence of anemia, which may represent the only clinical sign of undiagnosed ABG.¹⁴

The pathogenetic event responsible for the clinical relationship between AITD and ABG remains to be elucidated. The close association with various autoimmune diseases and the presence in familial clusters of AITD and

ABG suggest an immunological cross-reaction.^{1,2,4,7} In this respect, Elisei et al,³⁰ by comparing the sequence of the gastric parietal cell antigen with that of thyroid peroxidase, found a homologous 11-residue peptide in both proteins; on these grounds, these researchers suggested the existence of an epitope common to thyroid peroxidase and the gastric parietal cell antigen, which had previously been identified as the hydrogen-potassium adenosine triphosphatase, the acid-producing structure of the stomach.³¹ However, the role of antiperoxidase antibodies in the pathogenesis of AITD is, as yet, unclear.¹⁶ Moreover, the role of cross-reactive antibodies in the pathogenesis of coexisting thyroid and gastric autoimmune diseases has been excluded,³² and the pathogenesis of ABG is not exclusively of autoimmune origin.³³ Thus, the correlation between AITD and ABG is clinically evident but as yet pathogenetically undefined.

In conclusion, data emerging from the present investigation indicate that about one third of patients with AITD have histologically and functionally proved ABG; ABG can be present even in young (<40 years) patients; the presence of ABG is not related to the clinical status of the AITD; the measurement of plasma gastrin levels represents the most reliable tool in the diagnosis of ABG in patients with AITD; and in patients with AITD, the presence of unexplained anemia, not necessarily PA, is highly suggestive of the presence of undiagnosed ABG.

Accepted for publication December 21, 1998.

This study was supported by grant 05/15/01/10 from the Ministero Università e Ricerca Scientifica e Tecnologica (1995-1996); and the Institute of Experimental Medicine of the National Research Council, Rome, Italy.

We thank Jens H. Rehfeld, PhD, for providing antibody 4562.

Preliminary results of this study were presented at the 11th International Thyroid Congress, Toronto, Ontario, September 16, 1995.

We thank Marian Shields, MD, for help with the linguistic style in the preparation of the manuscript.

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