

# Early Manifestations of Gastric Autoimmunity in Patients with Juvenile Autoimmune Thyroid Diseases

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Juvenile patients affected with autoimmune thyroid disorders showed a 14–21% prevalence of parietal cell antibodies (PCA) reacting against the H<sup>+</sup>/K<sup>+</sup>-ATPase of the gastric parietal cells. PCA are the principal immunological markers of atrophic body gastritis (ABG).

ABG is characterized by loss of oxyntic glands, achlorhydria, and hypergastrinemia. The aim of this study was to determine whether PCA positivity could be associated with biochemical and histological manifestations of gastric autoimmunity in juvenile patients with autoimmune thyroid disease (AITD). We studied 129 children (96 females and 33 males) with chronic lymphocytic thyroiditis (n = 115) or Graves' disease (n = 14). Mean age at diagnosis of AITD was 9.7 ± 3.3 yr, and mean age at sampling was 12.3 ± 3.7 yr.

We determined PCA and *Helicobacter pylori* antibodies, gastrin, and pepsinogen I plasma levels. Gastroscopy with multiple biopsies was carried out in a subgroup of patients with PCA positivity. We found that 30% of children had detectable PCA. Hypergastrinemia was found in 45% of the PCA-positive children (range, 40–675 pg/ml) vs. 12% of PCA-negative children (range, 35–65 pg/ml; P < 0.001). Eighteen patients with PCA positivity underwent gastroscopy; eight of these children had normogastrinemia, which showed no signs of ABG, and 10 children had hypergastrinemia, of whom five had mild to severe ABG. Our study shows that autoimmune gastritis is an early event in juvenile AITD with detectable PCA. Gastrin plasma level is a reliable marker of gastric atrophy. (*J Clin Endocrinol Metab* 89: 4944–4948, 2004)

**A**UTOIMMUNE THYROID DISEASES (AITD), including chronic lymphocytic thyroiditis (CLT) and Graves' disease (GD), are organ-specific autoimmune disorders defined by lymphocytic infiltration of the thyroid (1). Autoantibodies to thyroid antigens [*i.e.* thyroid peroxidase antibody (TPOAb), antithyroglobulin antibody (TgAb), and anti-TSH-receptor antibody (TRAb)] are usually detectable in serum (2).

Atrophic body gastritis (ABG; formerly known as type A) is a chronic gastritis affecting the corporal mucosa. It is characterized by disappearance of oxyntic glands and loss of production of chlorhydric acid and intrinsic factor (3, 4). Hypoachlorhydria causes loss of feedback on gastrin production, thus hypergastrinemia and low pepsinogen I serum levels are well-established biochemical markers of ABG in adult patients (5).

ABG increases the risk of gastric cancer (6) and carcinoid tumors (7) and can be associated with iron deficient anemia (8) and pernicious anemia (9).

An autoimmune etiology has been recognized among the causes of ABG (4). Parietal cell antibodies (PCA) reacting against the H<sup>+</sup>/K<sup>+</sup>-ATPase of the gastric parietal cells (10) are considered the principal immunological marker of ABG.

In unselected populations, ABG and pernicious anemia are

more common in the elderly (11, 12). However, adult patients affected with autoimmune diseases, such as type 1 diabetes (13), and AITD (14) have been shown to have a high prevalence of ABG and manifestations of related gastric disorders at a younger age.

Juvenile patients affected with AITD showed a 14–21% prevalence of PCA (15, 16). ABG has been reported in childhood (17), but no detailed data related to gastric histology and gastric function have recently been reported in these patients. To our knowledge, only one study has addressed gastric disorders in juvenile AITD (18). In this study, the authors found that two of 31 children had ABG at histological examination. However, gastrin and pepsinogen I serum levels were not reported.

We wondered whether, in juvenile patients affected with AITD, the determination of PCA antibodies and of serological markers of gastric damage, such as gastrin and pepsinogen I, could help identify patients with early onset of autoimmune gastropathy manifestations.

## Patients and Methods

We studied 129 consecutive children (96 females and 33 males) with CLT (n = 115) or GD (n = 14). All the patients were from the Pediatric Endocrinology Division of "La Sapienza" University and were admitted for thyroid disease. All children and parents were interviewed according to a standard questionnaire (19) to define the presence and the severity of dyspeptic symptoms that were experienced during the 4 wk before study entry. The questionnaire took into account the following symptoms: abdominal (epimesogastric) pain, early satiety or anorexia, feeling of fullness (or bloating), and regurgitation (or vomiting or heartburn). No gastrointestinal symptoms or disorders (besides known celiac disease) were referred at the entry into the study. Written informed consent was obtained from parents and children. This study was approved by the ethical committee of our institution.

Abbreviations: ABG, Atrophic body gastritis; AITD, autoimmune thyroid disease; CLT, chronic lymphocytic thyroiditis; GD, Graves' disease; HpAb, *Helicobacter pylori* antibody; PCA, parietal cell antibodies; TgAb, antithyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, anti-TSH-receptor antibody.

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CLT was defined on the basis of the presence of thyroid autoantibodies [antiperoxidase (TPOAb) and/or antithyroglobulin (TgAb)] and thyroid ultrasound showing reduced echogenicity compatible with thyroiditis, regardless of the thyroid function.

GD was defined by clinical and biochemical hyperthyroidism and by positivity of TRAb. Free T<sub>3</sub>, free T<sub>4</sub>, TSH, TPOAb, and TgAb serum levels were determined in all patients. TRAbs were determined in presence of hyperthyroidism. All patients underwent thyroid ultrasound.

Among the 129 children with AITD, 14 (10.8%) had type 1 diabetes, and seven (5.4%) had celiac disease. The mean age at diagnosis of AITD was  $9.7 \pm 3.3$  yr, and the mean age at sampling was  $12.3 \pm 3.7$  yr.

PCA and *Helicobacter pylori* antibodies (HpAb) in serum were determined in all patients, and gastrin and pepsinogen I plasma levels were determined in all but 12 patients (91%). We selected children to undergo gastroscopy only on the basis of PCA positivity because of the invasiveness of gastroscopy and the need for sedation.

All children (and/or parents) with PCA positivity were asked to undergo gastroscopy. Gastroscopy with multiple biopsies was carried out in 18 patients with PCA positivity; 10 of these patients had associated hypergastrinemia, and eight had normal gastrin plasma levels. The other children (and/or parents) refused to undergo this procedure because it was too invasive.

Thyroid hormones and thyroid autoantibodies in serum were determined by commercial kits. Free T<sub>3</sub> and free T<sub>4</sub> were determined by RIA, TSH (upper normal value, 3.5  $\mu$ U/ml) was determined by immunoradiometric assay (all by Byk-Sangtec Diagnostica, Dietzbach, Germany), TRAb was determined by radioreceptor assay (Radim, Angleur, Belgium), and TPOAb and TgAb were determined by immunoradiometric assay (ICN Pharmaceuticals Inc., Costa Mesa, CA). Fasting gastrin levels were evaluated in plasma by means of a specific RIA using antibody no. 4562 (Prof. J. F. Rehfeld, Copenhagen, Denmark), as described earlier (20). Normal reference values were 0–30 pg/ml.

*H. pylori* IgG antibodies were determined using an ELISA commercial kit (G.A.P. test IgG; Bio-Rad, Milan, Italy) as previously reported (21, 22). The positive cutoff value for *H. pylori* IgG was more than 12.5 IU/liter. Pepsinogen I levels were measured using a commercial RIA kit (Pepsik; Sorin, Saluggia, Italy) as reported elsewhere (21, 22). The normal reference values in our laboratory are 20–80 ng/ml. PCA were determined in serum using a solid phase immunosorbent assay commercial kit (AUTOSTAT; Cogent Diagnostic Ltd, Edinburgh, Scotland, UK) (U/ml, normal value negative) with a variation coefficient of 9.8% in our laboratory (21, 22).

Upper gastrointestinal endoscopy was performed with an Olympus 130 videoendoscope (diameter, 8.5 mm; biopsy channel diameter, 2.8 mm) (Olympus, Tokyo, Japan) after iv sedation with meperidine (1–2 mg/kg) and midazolam (0.05 mg/kg up to a maximum of 0.2 mg/kg or 5 mg). At least six biopsy samples for conventional histopathological examination were obtained by using forceps (diameter, 2.2 mm). At least two biopsies were taken from each of the following areas: from the gastric antrum within 2 cm from the pylorus; from the greater curve of the midbody of stomach; and from the gastric fundus. The pathologist was blinded for clinical and laboratory data. The degree of gastritis was assessed according to the Updated Sydney System (4). Atrophy of the gastric body mucosa was defined as focal or complete oxyntic gland loss and/or replacement by metaplastic pylori or intestinal glands. To each graded variable, the following scores were assigned: 0 for absence, and 1, 2, or 3 for mild, moderate, or severe degrees, respectively, as previously reported (23).

### Statistics

Data were expressed as mean  $\pm$  SEM and evaluated by appropriate statistical tests (*t* test for paired data or Wilcoxon test). Analyses were performed using parametric statistical tests (*t* test for paired data) and nonparametric statistical tests (Mann-Whitney). Fisher's exact test and the  $\chi^2$  test were used when appropriate. *P* < 0.05 was considered statistically significant.

## Results

### Prevalence of PCA antibodies

We found that 39 (30%) of 129 children had PCA-detectable antibodies. The PCA-positive children (group 1) and the

PCA-negative children (group 2) were comparable for mean age at diagnosis of AITD, mean age at sampling, female to male ratio, prevalence of other autoimmune diseases, and percentage of HpAb positivity. The clinical characteristics of the PCA-positive compared with the PCA-negative children are summarized in Table 1.

We found that eight (57%) of 14 children with GD had detectable PCA vs. 31 (27%) of 115 children with CLT. This difference was statistically significant (*P* = 0.03).

Among children with CLT, 22 (71%) of 31 PCA-positive children vs. 42 (50%) of 84 PCA-negative children underwent treatment for subclinical or clinical hypothyroidism. Although this difference was not statistically significant, a trend was observed (*P* = 0.06).

No differences in hematological parameters (hemoglobin, ferritin, and mean corpuscular volume) were found between the two groups (data not shown).

### Gastrin and pepsinogen I levels

Gastrin and pepsinogen I levels were determined in 33 (85%) of 39 patients from group 1 (PCA positive) and in 84 (93%) of 90 patients in group 2 (PCA negative). Results are summarized in Table 2.

We demonstrated hypergastrinemia in 15 (45%) of 33 children (range, 40–675 pg/ml) from group 1 (PCA positive) vs. 10 (12%) of 84 children (range, 35–65 pg/ml) from group 2 (PCA negative) (*P* < 0.001,  $\chi^2$  test).

Plasma gastrin levels were found to be higher in the PCA-positive group (mean  $\pm$  SEM, 80.3  $\pm$  27.3 pg/ml) compared with the PCA-negative group (mean  $\pm$  SEM, 21.8  $\pm$  1.2 pg/ml). The difference was highly significant (*P* < 0.001).

When we excluded children with HpAb positivity from both groups (group 1, *n* = 8; and group 2, *n* = 19), we found that gastrin levels persisted significantly higher in PCA-positive children compared with PCA-negative children (92.2  $\pm$  37.5 vs. 21.2  $\pm$  1.2 pg/ml, respectively; *P* = 0.002).

Mean pepsinogen I levels were 40.9  $\pm$  3.9 ng/ml in the PCA-positive group and 42.0  $\pm$  1.8 ng/ml in the PCA-negative group (*P* = not significant). Low pepsinogen level was found in four (12%) of 33 PCA-positive children (range, 0–16 ng/ml), whereas only two (2%) of 84 PCA-negative children had a pepsinogen I value just below the lower normal range (e.g. 17–18 ng/ml) (*P* = not significant).

**TABLE 1.** Clinical characteristics of PCA+ and PCA– children

	PCA+	PCA–	<i>P</i>
<i>n</i>	39	90	
Female/male	33/6	63/27	NS
Age at diagnosis AITD yr	9.2 $\pm$ 3.5	9.9 $\pm$ 3.4	NS
Age at sampling yr	12.3 $\pm$ 3.8	12.1 $\pm$ 3.7	NS
CLT	31 (27%)	84 (73%)	
GD	8 (57%)	6 (43%)	
Associated autoimmune disease	6 T1DM/1CD (18%)	8 T1DM/6 CD (15.5%)	NS
HpAb+	8/39 (20.5%)	21/90 (23.3%)	NS

T1DM, Type 1 diabetes mellitus; CD, celiac disease; NS, not significant. Data are expressed as mean  $\pm$  SD.

### Histological findings

Gastroscopy with multiple biopsies was carried out in 18 patients with PCA positivity; they represented 46% (18 of 39) of the PCA-positive patients but only 14% (18 of 129) of the study population. The histological findings in the 18 children with detectable PCA who underwent gastroscopy are illustrated in Table 3 (including 10 children with hypergastrinemia) and Table 4 (including eight children with normogastrinemia). These two groups were comparable for female to male ratio, age at diagnosis of AITD, age at sampling, PCA titers, percentage of HpAb positivity, pepsinogen I plasma levels, and hematological parameters. The difference between the mean gastrin plasma levels in the two groups was extremely significant ( $P < 0.0001$ ; Tables 3 and 4).

In the 10 children with hypergastrinemia and PCA positivity (Table 3), we found three children with chronic superficial pangastritis involving the antrum and the corpus. Histology for *H. pylori* was positive in all three patients, and all three patients had HpAb detectable in serum. Gastrin plasma levels were slightly elevated, and pepsinogen I levels were in the normal range.

We found five of 10 patients with ABG; three of them had severe atrophy (grade 3), and one had moderate atrophy

(grade 2). The HpAbs were negative. These four patients showed severe hypergastrinemia combined with low to absent pepsinogen levels. The remaining child showed mild atrophy (grade 1) with mild hypergastrinemia. The last two children with slight hypergastrinemia had no evidence of *H. pylori* gastritis or gastric atrophy.

To investigate children with detectable PCA but normal gastrin plasma levels, eight children underwent gastroscopy (Table 4). Two of eight children showed chronic superficial pangastritis and were *H. pylori* positive, with HpAb detectable in serum; the remaining six had no evidence of gastric atrophy on histological examination.

### Discussion

This study shows a PCA prevalence of 30% in juvenile patients affected with AITD and demonstrates that 45% of these children and adolescents had mild to severe hypergastrinemia. Thus, the prevalence of PCA in these patients is much higher than that reported in normal children aged 0–15 yr (0.3%) (24).

We found a higher prevalence of PCA in our juvenile AITD patients compared with the PCA prevalence of 14–21% reported in previous studies (15, 16). However, we used a

**TABLE 2.** Gastrin and pepsinogen I plasma levels

	PCA+ (n = 33)	PCA- (n = 84)	P
Gastrin (pg/ml)	80.3 ± 27.3	21.8 ± 1.2	<0.001
Gastrin in HPAb-	92.2 ± 37.5 (n = 25)	21.2 ± 1.2 (n = 65)	0.002
Gastrin in HPAb+	43.1 ± 14 (n = 8)	23.9 ± 3.3 (n = 19)	NS
Gastrin > 30 pg/ml	15/33 (45%)	10/84 (12%)	<0.001
Pepsinogen I (ng/ml)	40.9 ± 3.9	42.8 ± 1.8	NS
Pepsinogen I <20 ng/ml	4/33 (12%)	2/84 (2%)	NS

Normal values: gastrin, <30 pg/ml; pepsinogen I, 20–80 ng/ml.

Data are expressed as mean ± SEM. NS, Not significant.

**TABLE 3.** Clinical, functional, and histological data of hypergastrinemic patients

Patient	Sex	AITD	Age at diagnosis AITD (yr)	Age at sampling (yr)	PCA [U/ml (nv neg)]	HpAb [IU/liter (nv < 12.5)]	Gastrin [pg/ml (nv < 30)]	Pepsinogen I [ng/ml (nv 20–80)]	Hb (gr%)	Mcv (μ3)	Ferritin (ng/ml)	Pathology
1	M	CLT	11	16	17	27	45	46	15.8	94	36	Chronic superficial pangastritis Hp+
2	M	CLT <sup>a</sup>	14	14	23	28	40	50	15.9	87	40	Chronic superficial pangastritis Hp+
3	F	CLT <sup>a</sup>	6	9	50	18	40	48	12.7	81	29	Chronic superficial pangastritis Hp+
4	F	GD	12	24	138	<12.5	140	16	8.6	62	3	Corpus predominant atrophic gastritis (++) <sup>b</sup>
5	F	CLT	7	8	113	<12.5	675	10	13.9	86	13	Corpus predominant atrophic gastritis (+++) <sup>b</sup>
6	F	CLT <sup>a</sup>	14	20	127	<12.5	>500	0	13.4	85	12	Corpus predominant atrophic gastritis (+++) <sup>b</sup>
7	F	CLT	14	16	105	<12.5	>500	0	15	88	24	Corpus predominant atrophic gastritis (+++) <sup>b</sup>
8	F	GD	7	14	108	<12.5	80	68	11	83	9	Corpus predominant atrophic gastritis (+) <sup>b</sup>
9	F	CLT	13	15	41	<12.5	40	40	13	90	9	Normal
10	F	GD	5	8	35	<12.5	40	42	12.6	86	35	Normal
Mean			10.3	14.4	75.7		210.0	32.0	13.1	84.2	21.0	
SD			3.6	5.1	46.6		246.9	23.6	2.2	8.5	13.3	
P <sup>c</sup>			NS	NS	NS		<0.0001	NS	NS	NS	NS	

M, Male; F, female; nv, normal value; Hp+, *H. pylori* positive; Hb, hemoglobin; Mcv, mean cell volume; NS, not significant.

<sup>a</sup> Associated type 1 diabetes mellitus.

<sup>b</sup> Corpus predominant atrophic gastritis degree: +, mild; ++, moderate; +++, severe.

<sup>c</sup> Comparing patients in Table 3 (hypergastrinemic) vs. patients in Table 4 (normogastrinemic).

**TABLE 4.** Clinical, functional, and histological data of normogastrinemic patients

Patient	Sex	AITD	Age at diagnosis AITD (yr)	Age at sampling (yr)	PCA [U/ml (nv neg)]	HpAb [IU/liter (nv < 12.5)]	Gastrin [pg/ml (nv < 30)]	Pepsinogen I [ng/ml (nv 20–80)]	Hb (gr%)	Mcv ( $\mu$ 3)	Ferritin (ng/ml)	Pathology
1	F	CLT	8	12	15	<12.5	25	46	11.5	75	6	Normal
2	F	CLT	3	10	21	<12.5	15	30	11.8	89	59	Normal
3	F	CLT	13	14	55	23	10	26	12.8	86	10	Chronic superficial pangastritis Hp+
4	F	GD	7	12	16	<12.5	25	34	13.5	82	31	Normal
5	F	GD	10	13	43	<12.5	25	34	13.8	82	33	Normal
6	M	CLT	8	13	35	<12.5	20	48	14.9	87	ND	Normal
7	F	CLT <sup>a</sup>	15	24	48	25	30	56	12.7	81	35	Chronic superficial pangastritis Hp+
8	M	GD	8	12	112	<12.5	30	40	14.9	82	22	Normal
Mean			9.0	13.7	43.1		22.5	39.2	13.2	83	28	
SD			3.7	4.3	31.6		7.0	10.1	1.2	4.3	17.7	
P <sup>b</sup>			NS	NS	NS		<0.0001	NS	NS	NS	NS	

F, Female; M, male; nv, normal value; Hp+, *H. pylori* positive; Hb, hemoglobin; Mcv, mean cell volume; ND, not determined; NS, not significant.

<sup>a</sup> Associated type 1 diabetes mellitus.

<sup>b</sup> Comparing patients in Table 3 (hypergastrinemic) *vs.* patients in Table 4 (normogastrinemic).

quantitative assay (25) to detect PCA, which makes it difficult to compare the prevalence of PCA determined by different methods.

Differences in race and age have been previously reported to be associated with PCA positivity (15). In the children with CLT and detectable PCA, 71% were hypothyroid *vs.* 50% of the PCA-negative children. A similar trend has been reported by Bright *et al.* (15). We found that patients with GD had a PCA positivity of 57%. An increased association of GD and pernicious anemia has been previously described in adults (26). It also has been reported that, in experimental animal models, thyroid function may influence the expression of gastric autoimmunity (27).

Hypergastrinemia was detected in 45% of our patients selected on the basis of PCA positivity. Hypergastrinemia suggests an early damage of the gastric oxyntic mucosa. Antral G cells secrete high levels of gastrin in response to lack of acid inhibitory feedback due to the loss of the oxyntic glands from the corporal mucosa. In four cases, very high levels of gastrin were associated with the low or absent pepsinogen I levels and the histological findings of the stomach showing severe gastric corporal atrophy. ABG associated with autoimmune hypothyroidism has been reported in children as young as 10 yr of age (17).

Plasma gastrin determination is a very useful tool in selecting children to submit to gastroscopy. Although a limited number of children were examined, we did not find gastric atrophy in children with plasma gastrin levels in the normal range. On the contrary, the highest gastrin levels were found in association with low or absent pepsinogen I and with gastric corporal atrophy at histological examination. However, it should be pointed out that, because only a subset accounting for 14% of the study population underwent gastroscopy (due to ethical reasons), the present findings should not be generalized until further studies confirm the present data. Due to the invasiveness of gastroscopy and the need of sedation in pediatric patients, we limited our study to PCA-positive patients, and we were able to perform gastroscopy only in 46% of PCA-positive patients. Thus, we have no

information about the risk of presenting gastric autoimmunity in PCA-negative patients with AITD.

To our knowledge, very few studies have addressed gastric disorders in juvenile AITD. Kuitunen *et al.* (18) reported two cases of gastric atrophy out of 31 children with autoimmune thyroiditis and nongoitrous juvenile hypothyroidism. The prevalence of PCA was 22%. In this study, however, gastrin and pepsinogen I were not determined, but five children had hypoachlorhydria. Hypergastrinemia associated with PCA positivity was reported by Kokkonen (28) in children affected with type 1 diabetes. We did not find evidence of any association between HpAb positivity and PCA positivity in our patients. The percentage of HpAb-positive cases was not significantly different between PCA-positive and -negative children.

In children and adolescents selected on the basis of *H. pylori* infection, the prevalence of gastric autoantibodies has been reported from 0–18% (29, 30).

In young subjects with a high susceptibility to develop autoimmune disorders, such as children with AITD, the role of *H. pylori* infection in triggering or causing ABG may be different from adult individuals who have ABG primarily linked to *H. pylori* infection (22).

This concept has been recently confirmed by the studies of De Block *et al.* (31, 32). They studied a large group of adult patients with type 1 diabetes and found no effect of *H. pylori* infection on the degree of corpus atrophy. Moreover, they reported that PCA positivity and hypergastrinemia, but not *H. pylori* infection, are risk factors for autoimmune gastritis (31, 32). It is noteworthy that they also found a prevalence of about 26% of (pre)malignant gastric lesions in these relatively young patients with detectable PCA (32).

In conclusion, our study shows that autoimmune gastritis is an early event in juvenile patients with AITD and detectable PCA. Because of the lack of symptoms, such patients should be screened for PCA and biochemical markers of gastric damage such as gastrin. Measurement of gastrin plasma levels is useful to select patients to be further investigated by gastroscopy. We suggest screening for PCA pa-

tients with AITD at diagnosis and determining gastrin in the presence of detectable PCA every year. We also suggest performing gastroscopy with multiple biopsies in the presence of PCA and hypergastrinemia and observing patients with ABG and performing gastroscopy in these patients every 5 yr as suggested for adult subjects (33). Finally, we suggest determining PCA every 2 years in PCA-negative patients with AITD because gastric autoimmunity can occur at any age.

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### References

- Delemarre FG, Simons PJ, Drexhage HA 1996 Histomorphological aspects of the development of thyroid autoimmune diseases: consequences for our understanding of endocrine ophthalmopathy. *Thyroid* 6:369–377
- Rapoport B, McLachlan SM 2001 Thyroid autoimmunity. *J Clin Invest* 108:1253–1259
- Dixon MF 1999 The Components of gastritis. Histology and pathogenesis. In: Graham DY, Genta RM, Dixon MF, eds. *Gastritis*. Philadelphia: Lippincott Williams & Wilkins; 51–66
- Dixon MF, Genta RM, Yardley JH, Correa P 1996 Classification and grading of gastritis. The Updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 10:1161–1181
- Kekki M, Samloff IM, Varis K, Ihämäki T 1991 Serum pepsinogen I and serum gastrin in the screening of severe atrophic corpus gastritis. *Scand J Gastroenterol Suppl* 186:109–116
- Hsing AW, Hansson LE, McLaughlin JK, Nyren O, Blot WJ, Ekbbom A, Fraumeni Jr JF 1993 Pernicious anemia and subsequent cancer. A population-based cohort study. *Cancer* 71:745–750
- Kokkola A, Sjoblom SM, Haapiainen R, Sipponen P, Puolakkainen P, Järvinen H 1998 The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anemia: a prospective follow-up study. *Scand J Gastroenterol* 33:88–92
- Marignani M, Delle Fave G, Mecarocci S, Bordi C, Angeletti S, D'Ambra G, Aprile MR, Corleto VD, Monarca B, Annibale B 1999 High prevalence of atrophic body gastritis in patients with unexplained microcytic and macrocytic anemia. *Am J Gastroenterol* 94:766–772
- Toh BH, Van Driel IR, Gleeson PA 1997 Pernicious anemia. *N Engl J Med* 337:1441–1448
- Karlsson FA, Burman P, Loof L, Mardh S 1988 Major parietal cell antigen in autoimmune gastritis with pernicious anemia is the acid-producing H<sup>+</sup>, K<sup>+</sup> adenosine triphosphatase of the stomach. *J Clin Invest* 81:475–479
- Villako K, Siurala M 1981 The behaviour of gastritis and related conditions in different populations. *Ann Clin Res* 13:114–118
- Carmel R 1996 Prevalence of undiagnosed pernicious anemia in the elderly. *Arch Intern Med* 156:1097–1100
- De Block CEM, De Leeuw IH, Van Gaal LF 1999 High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. *J Clin Endocrinol Metab* 84:4062–4067
- Centanni M, Marignani M, Gargano L, Corleto VD, Casini A, Delle Fave G, Andreoli M, Annibale B 1999 Atrophic body gastritis in patients with autoimmune thyroid disease. *Arch Intern Med* 159:1726–1730
- Bright GM, Blizzard RM, Kaiser DL, Clarke WL 1982 Organ-specific autoantibodies in children with common endocrine disease. *J Pediatr* 100:8–14
- Neufeld M, Maclaren N, Blizzard R 1980 Autoimmune polyglandular syndromes. *Pediatr Ann* 9:154–163
- Vaterlaws AL 1969 Gastric atrophy in childhood. *Arch Dis Child* 44:710–714
- Kuitunen P, Mäenpää, J, Krohn K, Visakoeri K 1971 Gastrointestinal findings in autoimmune thyroiditis and non-goitrous juvenile hypothyroidism in children. *Scand J Gastroenterol* 6:335–341
- Cucchiara S, Franzese A, Salvia G, Alfonsi L, Iula VD, Montisci A, Moreira FL 1998 Gastric emptying delay and gastric electrical derangement in IDDM. *Diabetes Care* 21:438–443
- Delle Fave G, Kohn A, De Magistris L, Annibale B, Bruzzone R, Sparvoli C, Severi C, Torsoli A 1983 Effects of bombesin on gastrin and gastric secretion in patients with duodenal ulcer. *Gut* 24:231–235
- Annibale B, Negrini R, Caruana P, Lahner E, Grossi C, Bordi C, Delle Fave GC 2001 Two thirds of atrophic body gastritis have evidence of *Helicobacter pylori* infection. *Helicobacter* 6:225–233
- Annibale B, Marignani M, Azzoni C, D'Ambra G, Caruana P, D'Adda T, Delle Fave G, Bordi C 1997 Atrophic body gastritis: distinct features associated with *Helicobacter pylori* infection. *Helicobacter* 2:57–64
- Bordi C, Annibale B, Azzoni C, Marignani M, Ferraro G, Antonelli G, D'Adda T, D'Ambra G, Delle Fave G 1997 Endocrine cell growths in atrophic body gastritis. Critical evaluation of a histological classification. *J Pathol* 182:339–346
- Landin-Olsson M, Karlsson A, Dahlquist G, Blom L, Lernmark A, Sundkvist G 1989 Islet cell and other organ-specific autoantibodies in all children developing type 1 (insulin dependent) diabetes mellitus in Sweden during one year and in matched control children. *Diabetologia* 32:387–395
- Karlsson FA, Burman P, Löf L, Olsson M, Scheynius A, Mardh S 1987 Enzyme-linked immunosorbent assay of H<sup>+</sup>/K<sup>+</sup>-ATPase, the parietal cell antigen. *Clin Exp Immunol* 70:604–610
- Furszyfer J, McConahey WM, Kurland LT, Maldonado JE 1971 On the increased association of Graves' disease with pernicious anemia. *Mayo Clin Proc* 46:37–39
- Wang J, Griggs ND, Tung KSK, Klein JR 1998 Dynamic regulation of gastric autoimmunity by thyroid hormones. *Int Immunol* 10:231–236
- Kokkonen J 1980 Parietal cell antibodies and gastric secretion in children with diabetes mellitus. *Acta Paediatr Scand* 69:485–489
- Kolho KL, Jusufovic J, Miettinen A, Savilahti E, Rautelin H 2000 Parietal cell antibodies and *Helicobacter pylori* in children. *J Pediatr Gastroenterol Nutr* 30:265–268
- Faller G, Keller MK, Claeys D, Buderus S, Kuhlwein D, Reiche N, Kirchner T 2002 Prevalence and specificity of antigastric autoantibodies in adolescents infected with *Helicobacter pylori*. *J Pediatr* 140:68–74
- De Block CEM, De Leeuw IH, Bogers JJPM, Pelckmans PA, Ieven MM, Van Marck EAE, Van Hoof V, Maday E, Van Acker KL, Van Gaal LF 2002 *Helicobacter pylori*, parietal cell antibodies and autoimmune gastropathy in type 1 diabetes mellitus. *Aliment Pharmacol Ther* 16:281–289
- De Block CEM, De Leeuw IH, Bogers JJPM, Pelckmans PA, Ieven MM, Van Marck EAE, Van Acker KL, Van Gaal LF 2003 Autoimmune gastropathy in type 1 diabetic patients with parietal cell antibodies. *Diabetes Care* 26:82–88
- Armbrrecht U, Stocbrugger RW, Rode J, Menon GG, Cotton PB 1990 Development of gastric dysplasia in pernicious anemia: a clinical and endoscopic follow up study of 80 patients. *Gut* 31:1105–1109

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