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Review

# Diagnosis and classification of autoimmune gastritis

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ABSTRACT

Autoimmune gastritis is a silent and highly prevalent disease that only becomes clinically manifested with progression to corpus atrophy and development of iron deficient or B12-deficient (pernicious) anaemia. Autoimmune gastritis is associated with autoimmune thyroiditis and type 1 diabetes mellitus. Corpus atrophy may be complicated by gastric carcinoids and gastric cancer. Laboratory diagnosis of autoimmune gastritis rests on serum biomarkers of antibody to parietal cell H/K ATPase and intrinsic factor and corpus atrophy on serum biomarkers of gastrin and pepsinogen levels. Subjects with asymptomatic parietal cell antibody should be regularly assessed for serum biomarkers for progression to corpus atrophy, development of iron and B12 deficiency anaemia and for associated autoimmune thyroiditis and type 1 diabetes mellitus.



**Contents**



## 1. Introduction

Autoimmune gastritis is a chronic inflammatory gastric disease limited to the fundus and body of the stomach (Type A gastritis) [1,2] and distinct from antral gastritis (Type B gastritis) associated with *Helicobacter pylori* [3]. Autoimmune gastritis is silent and only becomes symptomatic years later when the inflammatory gastric lesion progresses to chronic atrophic gastritis that manifests as either B12-deficient pernicious anaemia [4,5] or antecedent iron deficiency anaemia [6]. The gastric lesion comprises of a chronic inflammatory infiltrate accompanied by cellular and humoral immune responses to gastric H/K ATPase. Gastric H/K ATPase-reactive CD4 T cells are major drivers of the autoimmune response in man and mice.

## 2. Epidemiology of autoimmune gastritis and chronic atrophic gastritis

The prevalence of autoimmune gastritis is unclear because it is asymptomatic, and inaccessible to detection save by gastric biopsy. Parietal cell antibody tested by ELISA was used as a biomarker for autoimmune gastritis in a population study of 9684 German subjects aged 50–74 years [7]. Parietal cell antibody was present in 19.5% of subjects and was strongly associated with pepsinogen biomarker for chronic atrophic gastritis but not with an antibody marker for *H. pylori*. In 429 individuals in the Canary islands, the prevalence of parietal cell antibody was 7.8% [8]. Thus, based on the serological biomarker of parietal

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cell antibody, the prevalence of autoimmune gastritis ranges from 7.8 to 19.5%.

Epidemiology of chronic atrophic gastritis is confounded by associated *H. pylori* infection. Development of corpus atrophy can be assessed by the serum gastrin concentration on its own or together with other biomarkers. A study of 1387 Northern Italian dyspeptic patients revealed a 94% correlation between a "GastroPanel" comprising tests for pepsinogen 1, pepsinogen 2 and gastrin-17 with atrophic gastritis identified by biopsy [9]. The prevalence of atrophic gastritis in this study was 10.7%. A study of 4256 Finnish volunteers using "GastroView panel" comprising tests for pepsinogen I and II levels (and ratio) as a biomarker for gastric atrophy and *H. pylori* IgG antibody level revealed positive tests for corpus atrophy in 3.5% increasing to 8% in those over 70 years with *H. pylori* infection in 37% [10]. The prevalence of atrophic gastritis thus appears to range from 3.5% to10.7%.

## 3. *H. pylori* and chronic atrophic gastritis

*H. pylori* is a common gastric pathogen affecting almost half the population of the world and is associated with Type B antral gastritis. Molecular mimicry between *H. pylori* antigens and gastric H/K ATPase has been invoked as a mechanism for the genesis of autoimmune gastritis [11]. The hypothesis is based on the observation that *H. pylori*-infected patients with autoimmune gastritis harbour gastric CD4 + T cells that recognize cross-reactive epitopes shared between gastric H/K ATPase and *H. pylori* proteins. Cross-reactive *H. pylori* peptides induced T cell proliferation and Th1 cytokine production and H/K ATPase autoantibodies were identified in 20–30% of *H. pylori* infected patients. *H. pylori* infection was found in a study of serum biomarkers of gastric atrophy (pepsinogen I, pepsinogen I/II and gastrin) and autoimmunity (parietal cell and intrinsic factor antibodies) in 23 patients with different grades of atrophic gastritis [12]. While these studies suggest a causative link they do not provide definitive evidence. Clearance of *H. pylori* infection with progression of gastritis to corpus atrophy [13] suggests a major underestimation of its association with chronic atrophic gastritis. A study of 25 patients with pernicious anaemia has also found that they were all negative for *H. pylori* antibody and *H. pylori* on gastric biopsy [14]. A "hit and run" hypothesis for *H. pylori* none-the-less remains possible where infection begins in the antrum but is lost with progression to corpus atrophy and loss of acid secretion. To test this hypothesis, a longitudinal study is required to document inception of *H. pylori* antral gastritis followed by extension to corpus autoimmune gastritis and loss of *H. pylori* infection with achlorhydria.

## 4. Haematological manifestations of autoimmune gastritis

With progression of autoimmune gastritis to gastric fibrosis and corpus atrophy, loss of intrinsic-factor producing gastric parietal cells leads to vitamin B12 malabsorption and megaloblastic pernicious anaemia [5]. Intrinsic factor antibody in the gastric juice that blocks intrinsic factor [15] may also contribute to the B12 deficiency. Pernicious anaemia is the commonest cause of vitamin B12 deficiency [16]. In a study of 729 persons aged 60 and older, 1.9% had unrecognized and untreated pernicious anaemia with a prevalence of 2.7% in women and 1.4% in men [17]. While this association is well recognized as an outcome of end-stage gastritis which may take many years to develop [4], the association with iron-deficiency anaemia is not as well known. Gastric acid is required to maintain iron in its more readily absorbable ferrous state. Hershko et al. [6] drew attention to iron deficiency, as a complication of achlorhydria that may precede pernicious anaemia. Among 160 patients with autoimmune gastritis identified by strongly positive parietal cell antibodies and hypergastrinaemia, 83 subjects presented with iron deficiency anaemia, 48 with normocytic indices, and 29 with macrocytic anaemia. Compared with macrocytic patients, patients with iron deficiency anaemia were 21 years younger and were mostly women. All groups had a high prevalence of thyroid disease (20%) and diabetes (8%). Stratification by age cohorts from younger than 20 years to older than 60 years showed a regular and progressive increase in mean corpuscular volume, serum gastrin levels and decrease in cobalamin level. Prevalence of *H. pylori* infection progressively decreased from 87.5% at age younger than 20 years to 12.5% at age older than 60 years. The findings challenge the common notion that pernicious anaemia is a disease of the elderly and imply a disease starting many years before clinical cobalamin deficiency. Patients with unexplained iron-deficiency anaemia should be investigated for autoimmune gastritis and pernicious anaemia as autoimmune atrophic gastritis is encountered in 20–27% of patients with obscure, or refractory iron deficiency anaemia and is 4 to 6 times more common than celiac disease causing unexplained iron deficiency [18]. These clinical features of iron deficiency anaemia associated with achlorhydria and mucosal corpus atrophy were accurately described as the "anaemia of achylia gastrica" by Faber and others over 100 years ago, including refractoriness to oral iron treatment, female predominance, relatively young age, increased prevalence of thyroid disease and progression to pernicious anaemia.

## 5. Associated autoimmune endocrinopathies

Reports of an association of pernicious anaemia with diabetes mellitus [19,20] was followed by reports of its association with thyroid autoimmunity, designated "thyrogastric autoimmunity" [21] and with vitiligo [22]. An association with primary hyperparathyroidism has been prospectively evaluated and confirmed to be 3-fold higher in 107 biopsy confirmed chronic atrophic gastritis [23].

Pernicious anaemia prevalence increased 3 to 5-fold with type 1 diabetes and autoimmune thyroiditis [24]. Gastric autoimmunity is present in up to a quarter and thyroid autoimmunity in up to a third of patients with type 1 diabetes. Relatives of diabetic patients, particularly mothers, have higher frequencies of these autoimmune conditions. A study of 97 children with type 1 diabetes followed up over 4 years also reported an association with gastric and thyroid autoimmunity [25]. In patients with autoimmune thyroiditis, gastric autoimmunity is present in a third and islet autoimmunity in a tenth [26]. These observations suggest that patients with these autoimmune diseases should be regularly screened as close follow-up of patients with organ-specific autoantibodies could lead to identification of those requiring therapy [27]. This suggestion is further supported by a study of 319 atrophic body gastritis patients, 169 (53%) of whom had associated thyroid disorder, and 89 (52.7%) of these were unaware of it [28]. The thyroid disease was autoimmune in 128 patients (75.7%). In 115 patients with autoimmune thyroid disease, 32 patients (28%) had low B12 levels, 8 out of 27 of these patients had parietal cell antibody and 8 out of 26 patients had elevated serum gastrin [29]. Gastric biopsy of 5 patients with high gastrin levels revealed atrophic gastritis.

Autoimmune gastritis can also develop with post-partum thyroiditis. In 54 women with postpartum thyroiditis [30], parietal cell antibodies to H/K-ATPase were found in 18 women during pregnancy and in 10 of them, a 2-9-fold increase in parietal cell antibody level was observed in the postpartum period. At 5-year follow-up, the initially parietal cell antibody-positive women still had elevated antibody levels. Hypergastrinaemia and low pepsinogen levels were noted in 4 women. In 2 of these women low serum vitamin B12 levels had developed. In 6 of 9 parietal cell antibody-positive women examined by gastroscopy, biopsy specimens from gastric body mucosa showed a chronic inflammatory infiltrate with microscopic evidence of atrophy in 3 patients.

Histologic evidence of autoimmune atrophic gastritis was obtained in 10 cases (15%) of 65 patients with vitiligo. These patients had gastric antibodies, elevated gastrin levels and gastric acid output after pentagastrin stimulation was markedly reduced [22]. The study provided definite evidence of an association of autoimmune atrophic gastritis with a proportion of vitiligo patients.

**Serum Biomarkers**

| Autoimmune gastritis | Chronic atrophic gastritis |
|---|---|
| • Parietal cell antibody to gastric H/K ATPase | • Gastrin |
| • Intrinsic factor antibody | • Pepsinogen |
| | • Ghrelin |

**Fig. 1.** Serum biomarkers for autoimmune gastritis and gastric atrophy.

## 6. Gastric carcinoids and gastric adenocarcinoma

Hypergastrinaemia arising from loss of HCl secreting gastric parietal cells drives development of antral enterochromaffin cell hyperplasia that can further develop into neoplasia and the carcinoid syndrome. Severely hyperplastic and dysplastic enterochromaffin cell hyperplasia are predictive of the development of neoplasia [31]. Gastroc carcinoids represent less than 10% of all carcinoid tumours and less than 1% of gastric neoplasms [32]. In 71 patients with pernicious anaemia followed up over 5.8 years, 8 gastric carcinoids (11.2%) were found with all but one removed endoscopically and no metastasis was found [33].

Among 877 Danish patients with gastric cancer, the diagnosis of pernicious anaemia was regarded as unquestionable in 12 patients (1.3%) [34]. Calculation of the incidence of gastric cancer in these patients showed that it was about three times higher than in the general population with an annual risk of gastric cancer of 0.3%. In pernicious anaemia patients, the tumour was primarily localized to the body and fundus of the stomach, whereas it mainly involved the antral and pyloric region in patients without pernicious anaemia. A systematic review of the global incidence also showed a pooled gastric cancer incidence-rate in pernicious anaemia of 0.27% per person-years and an estimated nearly sevenfold relative risk of gastric cancer in pernicious anaemia patients [35].

## 7. Serum biomarkers for autoimmune gastritis

Asymptomatic autoimmune gastritis is identified by parietal cell antibody. Studies of an Estonian rural population of 227 persons aged 15–79 years have shown that parietal cell antibody correlates with biopsy evidence of fundal gastritis [36]. During a 6 year followup of 199 persons, no significant changes in the state of the gastric fundic mucosa in relation to parietal cell antibody was found [37], consistent with the protracted course towards gastric atrophy [4]. Although parietal cell antibody identified by immunofluorescence continues to be used in diagnostic immunology laboratories, identification of gastric H/K ATPase as the molecular target for parietal cell antibody [38] has led to an ELISA for this antibody [39,40]. ELISA for gastric H/K ATPase is about 30% more sensitive than immunofluorescence for identification of parietal cell antibody, rises with age and segregates with intrinsic factor antibody [41]. Sera that reacted to gastric H/K ATPase by ELISA but not with gastric parietal cells by immunofluorescence all reacted with both the α and β subunits of the gastric H/K ATPase by immunoblotting and rose proportionately with age with sera that were positive by immunofluorescence. In a study of 165 patients with biopsy-proven chronic atrophic gastritis and 113 controls, combining parietal cell antibody with intrinsic increased their diagnostic performance yielding 73% sensitivity for pernicious anaemia [42]. These findings are at variance with a study that found limited value for intrinsic factor antibody in patients who were negative for parietal cell antibody identified by immunofluorescence [43]. Of 847 samples identified in a retrospective study, 4 (0.47%) were positive for intrinsic factor antibodies only, 731 (86.3%) positive for parietal cell antibody alone, and 112 (13.2%) for both. In 91 consecutive patients with low B12 levels; all were negative for gastric parietal cell antibodies and intrinsic factor assay.

Parietal cell antibody identified by ELISA to gastric H/K ATPase predicted the development of chronic atrophic gastritis in a prospective 5 year study of 208 adults with autoimmune thyroid disease. Autoantibody levels rose progressively over time, peaked and then fell, following progressive gastric mucosal destruction and loss of target autoantigen [44]. Similar observations were reported by Carmel [45]. A positive parietal cell antibody and low pepsinogen 1 identified patients with a higher risk to cobalamin deficiency during follow-up in a 5-year prospective study of 186 patients with type 1 diabetes mellitus [46]. Thus parietal cell antibody is not only a diagnostic marker of autoimmune gastritis and but also a predictive marker of subsequent corpus atrophy and its haematological manifestations.

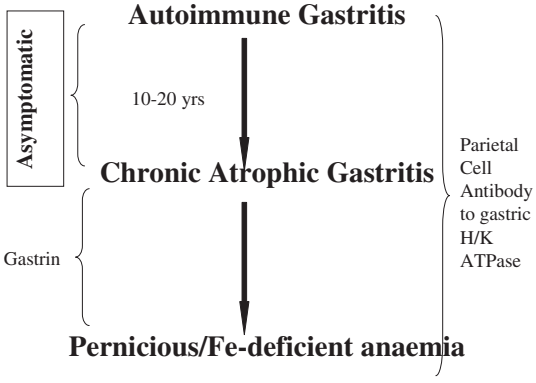


**Fig. 2.** Natural history of autoimmune gastritis and gastric atrophy.

## 8. Serum biomarkers for gastric atrophy

Serum biomarkers have been assessed to identify fundus atrophy without the need of gastric biopsy. These screening tests use a combination of pepsinogen 1 (P1), pepsinogen 2, pepsinogen1/pepsinogen 2 ratio and gastrin-17 to reliably identify the presence of chronic atrophic gastritis [47–49]. Loss of zymogenic cells leads to low pepsinogen levels while loss of acid secretion leads to hypergastrinemia. These serum biomarker were tests designated the "serological gastric biopsy". Combination of these tests for corpus atrophy with antibody to *H. pylori* identifies infection with this organism. In one study [48], PGI/PGII ratio gave the best sensitivity (96.1%) and negative predictive value (97.7%), PGI, the highest specificity (94.6%), PGII, a high negative predictive value (90.7%) but IgG anti-*H. pylori* showed poor sensitivity and specificity (58.8% and 26.5%, respectively). Concordance between these serum biomarkers and gastric biopsy is excellent [50]. A study of 309 biopsy-established cases has also validated the tests for pepsinogen I, pepsinogen II and gastrin-17 levels as serological tests for fundus atrophy [51].

Serum ghrelin produced by endocrine cells of the gastric mucosa is an emergent and promising new test for gastric atrophy. Serum ghrelin was reported to be associated with the highest sensitivity and specificity (97.3 and 100%, respectively) in detecting gastric atrophy and superior to pepsinogen I/II ratio and gastrin [52]. Plasma ghrelin levels correlated with serum levels of pepsinogen and decrease with the extent of atrophic change in gastric mucosa irrespective of *H. pylori* infection [53,54].

Fig. 1 summarizes serum biomarkers for autoimmune gastritis and corpus atrophy.

## 9. Laboratory management of autoimmune gastritis

Subjects with silent autoimmune gastritis identified by parietal cell antibody biomarker should be regularly monitored by serum biomarkers for progression to gastric corpus atrophy, iron deficiency and B12 deficiency anaemia (Fig. 2) and for associated autoimmune thyroiditis and type 1 diabetes mellitus. The 30% increased sensitivity of the ELISA over immunofluorescence for identification of parietal cell antibody [41] increases the likelihood of identification of asymptomatic autoimmune gastritis. While biennial endoscopy for gastric neoplasms does not appear useful for their detection [55], it has been suggested

that patients with extensive atrophic gastritis and/or extensive intestinal metaplasia should be offered endoscopic surveillance every 3 years [56].

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