Medicine is a lifelong education.

(Sir William Osler, 1848-1920)
Chapter V

Comparison between serology, endoscopy and histology in the diagnosis of advanced gastric body atrophy: a study in a Dutch primary care community

A. Korstanje¹, S. van Eeden¹, G.J.A. Offerhaus¹, F. L. Waltman¹, G. den Hartog¹, E.W.C. Roelands², J.H.M. Souverijn¹, I. Biemond², C.B.H.W. Lamers⁶.

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Abstract

Background: Gastric body atrophy (GBA) is a precursor lesion of gastric cancer. Little is known about the value of serological screening for GBA in a primary health care community.

Aim: To study the relation between serological findings, endoscopical and histological GBA changes in a sample of the general population.

Subjects & methods: Consecutive adults (n = 997) were serologically screened for GBA in a Dutch family practice. Thirty-four subjects had serological GBA defined as hypergastrinæmia (> 100 ng/l), hypopepsinogenæmia A (< 17 µg/l) and a low pepsinogen A/C ratio (< 1.6). Twenty-five subjects of this group, agreed in serological retesting and further investigation with gastroscopy and biopsy for assessment according to the Sydney system.

Results: At serological retesting 20 of 25 subjects again fulfilled the criteria of GBA. Histological examination of the corpus biopsies showed advanced GBA in 18 of 24 subjects (75%, 1 subject had no corpus biopsies) and 17 of 19 (89%) subjects with repeated positive serology. After disclosure of serology results, re-examination of the biopsies revealed GBA also in the 2 patients with initially insufficient

¹ General practice, 's-Gravenpolder, The Netherlands
² Department of Pathology, Academic Medical Centre, Amsterdam, The Netherlands
³ Department of Internal Medicine, Oosterschelde Hospital, Goes, The Netherlands
⁴ Department of Gastroenterology, Rijnstate Hospital, Arnhem, The Netherlands
⁵ Department of Clinical Chemistry, Leiden University Medical Centre, Leiden, The Netherlands
⁶ Department of Gastroenterology, Leiden University Medical Centre, Leiden, The Netherlands.
evidence of GBA, giving a concordance of 100% (19/19). One subject with normal serum gastrin at retesting, thus no longer fulfilling the serological criteria of GBA (false-negative), had both antral and body atrophy giving a concordance between serological and histological GBA of 95% (19/20). No adenomatous polyps, tumours or dysplastic alterations were found. Macroscopic features observed during gastroscopy were of no value in the assessment of atrophy.

Conclusions: Identification by serology of subjects with chronic atrophic body gastritis in population-based screening and prevention studies in primary care is adequately possible and useful in selecting subjects for endoscopy.

Introduction

Chronic atrophic gastritis is a chronic inflammation of the stomach accompanied by loss of the specialized glandular cells (1). Atrophy leads to thinning of the mucosa and is a common denominator in all pathological processes, causing severe mucosal damage. The development of chronic atrophic gastritis is a multifactorial process, involving microbiological factors like *Helicobacter pylori* infection, unidentified host and environmental factors, or autoimmunity directed against gastric glandular cells (1-4). The autoimmune form of gastritis is typically located in the body, whereas the type induced by chronic injury or infection is located more often in the antrum. The loss of the glandular structures can be accompanied by metaplasia.

A large number of studies point to the importance of chronic gastritis in the evolution of such gastritis towards mucosal atrophy, intestinal metaplasia, dysplasia and finally gastric adenocarcinoma (5-7). Early identification of patients with atrophic gastritis might give opportunities in modifying the risk of gastric cancer, which is nowadays the second leading cause of cancer-related mortality worldwide, having a very poor clinical prognosis (8). Histological examination is the most reliable way to determine atrophic gastritis, but this is not done routinely in patients without gastric cancer. Its principal use is to rule out the presence of cancer rather than to determine the presence and extent of atrophic gastritis. The by far preferable diagnostic instrument to screen for atrophic gastritis is a serum biopsy, i.e. measuring serum pepsinogen A and C and serum gastrin as functional markers of the gastric mucosa (9,10). Low serum pepsinogen A (PgA) and a low pepsinogen A/C ratio in combination with elevated serum gastrin, are considered useful predictors of gastric body atrophy (GBA). Several studies have shown the diagnostic potential of non-invasive, serological biomarkers for atrophic gastritis (11-14). Taking into account the underlying aetiology of chronic atrophic gastritis, serological testing for *H. pylori* (12,13) and parietal cell antibodies has an additional diagnostic value (14,14).

Apart from predisposing to gastric cancer, gastric body atrophy can also lead to vitamin B₁₂ deficiency. This occurs with both autoimmune corpus gastritis and
the more common multifocal pangastritis involving corpus and antrum that results from *H. pylori* infection. This can exist already for a long time as a clinical latent entity with possible irreversible cell damage to the nervous system \(^5\text{,}^{13}\). Early detection of vitamine B\(_{12}\)-deficiency is therefore important and timely supplementation is indicated to prevent pernicious anaemia and neurological sequelae. It is likely that a significant number of patients suffering from a deficiency of vitamine B\(_{12}\) caused by atrophic gastritis remain undiagnosed and untreated and that, with regard to public health, it would be important to identify these patients early enough \(^16\).

Despite the apparent importance of the diagnostic potential of serological methods, no studies have been conducted in general practice, so far, to determine the significance of serology in the screening for atrophic body gastritis. The purpose of the present study was to evaluate the value of the serological markers of atrophy, i.e. blood pepsinogen and gastrin levels, to predict histological GBA in a community-based family practice in The Netherlands. Additionally, attention was payed to the prevalence of *H. pylori* infection on the basis of serological tests and histological examination and to the prevalence of autoimmunity in gastric atrophy.

### Subjects and methods

#### Study Population

In a period of 2 years a total of 997 adults, consecutively entering the primary health-care system because of common medical problems, volunteered in serological screening for GBA in the general practice in ’s-Gravenpolder, a rural village in the South-West of The Netherlands. Exclusion criteria were age < 18 years, current pregnancy, gastric resection, renal insufficiency and the use of antisecretory agents. The participants were asked to donate a fasting blood sample and to fill in a questionnaire describing the frequency and severity of gastric symptoms during the preceding 3-month period, past gastric diseases and the use of stomach- and/or antibiotic drugs.

Examination of the whole group revealed serological GBA in 34 persons (3.4%, 15 M, 19 F; mean age 67 years, range 28–91).

Two years later, 25 of the 34 subjects (12 M, 13 F; mean age 67 years) agreed in undergoing upper gastrointestinal endoscopy after an overnight fast, combined with serological retesting of the markers of atrophy and *H. pylori*- and autoimmune serology. The remaining 9 subjects were not biopsied for the following reasons: 3 persons died of cardiovascular related diseases, 2 persons had moved out of the region, 2 persons were not able to undergo endoscopy because of serious not gastro-intestinal related comorbidity and 2 persons refused further investigation.

The study was performed according to the declaration of Helsinki and all participants gave informed consent before entering the study.
Serological examination
All obtained serum samples were tested by well-validated radio-immunoassays for levels of pepsinogen A (PgA), pepsinogen C (PgC) and gastrin. Our validated criteria for advanced serological GBA, corresponding to pentagastrine refractory achlorhydria or severe hypochlorhydria (peak acid output < 5 mmol/hr), expressed in the level of the serum markers, were a serum concentration of PgA < 17 µg/l, a PgA/C ratio < 1.6 and an accompanying serum concentration of gastrin > 100 ng/l.

H. pylori serology was performed by a validated enzyme immunoassay using specific immunoglobulin G against H. pylori. The results were expressed as the absorbance index (AI): serum with an AI > 0.32 IgG H. pylori antibody was considered evidence of H. pylori infection. Additionally, all serum samples were tested for parietal cell- and intrinsic factor autoantibodies using commercially available kits, respectively Autoscreen 1, Scimedx Corporation, Denville, NJ 07834, USA and Genesis Diagnostics Ltd, Little port, UK. Serum vitamine B<sub>12</sub> concentration was tested by Immulite Vitamin B<sub>12</sub>, Diagnostic Products Corporation, Los Angeles, CA 90045-5597, USA.

Endoscopic Examination
Patients fasted for at least 9 hours before the examination. Gastroscopy was performed in the usual manner using an Olympus video-endoscopy equipment. Endoscopic characteristics and appearances of gastric mucosal inflammation were recorded for each subject according to the Sydney System, Endoscopic division. The following characteristics were scored: normal mucosa with its pink colour, with uniform smoothness and lustre, versus endoscopic characteristics of inflammation e.g. 1. edema - 2. erythema - 3. friability - 4. exudates - 5. flat erosions - 6. raised erosions - 7. rugal hyperplasia - 8. rugal atrophy - 9. visibility of vascular pattern - 10. intramural bleeding spots - 11. nodularity. After maximum air insufflation at the end of examination, the corpus was examined for the presence of rugae. The grade of the various macroscopic features was scored as absent, mild, moderate or severe.

Biopsy Collection
Biopsy samples were obtained using a standard pinch-biopsy forceps. Antral and fundic biopsy specimens were systematically collected as follows: 6 biopsies from the mid antrum, about 2 cm pre-pyloric from the anterior and posterior antral wall, 4 for histological examination, 2 for culture; 6 biopsies from the mid body, about 5 cm distal of the oesophagus-cardia junction from the anterior and posterior body wall, also 4 for histological examination and 2 for culture. Biopsies for histology were fixed in 10% buffered formalin.

Histological Examination
All biopsies from each subject were routinely fixed in 10% buffered formalin and em-
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bedded in paraffin blocks. Five micron sections were hematoxylin and eosin stained and examined by 2 expert gastrointestinal pathologists (SvE & GJAO) according to the updated Sydney classification. Additional immunostaining was performed with antibodies against gastrin, chromogranin and \textit{H. pylori} to identify gastrin producing G-cells, enterochromaffin-like cells and \textit{H. pylori}, respectively. The diagnosis of chronic atrophic gastritis was based on the full spectrum of the updated Sydney System scores \cite{1,19}, i.e. chronic inflammation, activity, glandular atrophy, intestinal metaplasia and absence or presence of \textit{H. pylori}, systematically applied to the biopsy specimens. Chronic inflammation was evaluated on the basis of an increase of mononuclear cell infiltration of the lamina propria. Activity of gastritis was defined according to the presence or absence of intra-epithelial granulocytes. Gastric atrophy refers to the loss of the deeper specialized glands, i.e. in the body the parietal cells and secondly the chief cells. The loss of the glandular structures can be accompanied by metaplasia \cite{1}. All histopathological issues were semi-quantitatively graded as absent, mild, moderate or severe. The biopsy specimens were reviewed by the 2 above mentioned experienced pathologists. In case of disagreement the pathologists discussed the case to reach consensus.

Results

Retesting of serum markers of atrophy

Re-testing of the markers of atrophy, undertaken 2 years after the initial screening and immediately before endoscopy, revealed serological gastric body atrophy only in 20 subjects of the whole group of 25 (Table 1).

The 5 “drop-out” subjects showed the following serological characteristics: 1 subject (no. 8) had after retesting normal gastrin with low PgA and low ratio PgA/C, thus no longer fulfilling the serological criteria of GBA. The remaining 4 subjects showed after retesting normal serum pepsinogens and normal gastrin, of whom 2 persons (nos. 3 and 14) had borderline test results in the first round and the other 2 individuals (nos. 6 and 15) had an unexplained conversion to normal levels of the serum markers (Table 1).

Histopathologic findings (see Table 1)

As expected after serologically retesting, 4 individuals with normal serology (nos. 3,6,14,15) had no evidence of histological body atrophy, but only modest aspecific chronic inflammation. One subject (no. 8), with normal gastrin and low PgA with a low A/C ratio, thus partially fulfilling the criteria of serological body atrophy, had antral and body atrophy in the biopsies, so making the serological profile false negative.

Moderate to severe body atrophy was found in 17 of 20 subjects with repeated serological GBA. With regard to the other 3 subjects: from 1 subject (no. 4) only