



Chronic Gastritis - Clinical Relevance

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A B S T R A C T

The commonest cause of chronic gastritis (CG) is *Helicobacter pylori* (HP) infection; it affects about half the world population. The vast majority of the subjects with CG are asymptomatic. A definite diagnosis of CG gastritis is only possible with gastric mucosal biopsy. Chronic atrophic gastritis (CAG) with intestinal metaplasia increases the risk of gastric adenocarcinoma.

The separation of CAG gastritis with histamine fast achlorhydria (HFA) and mild vitamin B₁₂ malabsorption (5-10% on Schilling test) from pernicious anaemia (PA) with severe vitamin B₁₂ malabsorption (< 5% on Schilling test), on the basis of vitamin B₁₂ absorption test, is inaccurate. In patients with CG, vitamin B₁₂ absorption test in fasting state (without any stimulus) is not reproducible. Furthermore, the observations were made in a small number of patients, in the study recommending the separation of these two diseases.

Differentiation of CG with HFA from PA should be based on the absence or presence of intrinsic factor antibody (IFA) respectively, in serum or gastric juice of patients. The diagnosis of PA should be restricted to only those patients with IFA.

Eradication of HP in patients with CG is not recommended, as vast majority of subjects are asymptomatic, the disease progresses very slowly over several decades, multiple antibiotics required to eradicate HP have significant side-effects and eradication of HP in a large population, may not be always beneficial.

INTRODUCTION

Gastritis (acute or chronic) is defined as inflammatory response of the gastric mucosa to infections or irritants. In normal gastric mucosa, inflammatory cells (including neutrophils) are sparse and an increase in chronic inflammatory cells (lymphocytes, plasma cells) indicates chronic gastritis (CG).

CLASSIFICATION OF CHRONIC GASTRITIS

Various classifications of CG based on pathological, topographical, immunological and endoscopic parameters have been described.¹⁻⁸

Whitehead et al¹ classified CG according to (i) the site of mucosa involved: pyloric, body, cardiac, transitional, indeterminate, (ii) the degree of gastritis: superficial or atrophic, and (iii) the presence of metaplasia: pseudopyloric or intestinal.

The earliest immunological classification of CG was reported by Desai² and Desai and Antia.³ They described a new classification of CG with maximal emphasis on immunological parameters and divided CG into three types: Type I (simple gastritis): Absence of both parietal cell antibody (PCA) and intrinsic factor antibody (IFA) (e.g. post-operative or corrosive gastritis); Type II (chronic gastritis): Presence of PCA and absence of IFA; Type

III (pernicious anaemia) (PA): Presence of both PCA and IFA (Fig 1).

Strickland and Mackay⁴ classified two types of CG : Type A : (autoimmune) involves the fundus-body and antrum is spared. It is diagnosed by histamine-fast achlorhydria (HFA), hypergastrinemia and severe vitamin B₁₂ malabsorption (less than 5% on Schilling test). PCA are present in 95% and IFA in 75% of patients. Type B : Environmental gastritis (now HP associated) initially affects the antrum, with varying involvement of body mucosa later on. Serum gastrin, acid secretion and vitamin B₁₂ absorption are usually normal but occasionally hypochlorhydria or mild vitamin B₁₂ malabsorption (5 – 10 % on Schilling test) may be present. Initially, the authors wrongly reported absence of PCA which was subsequently corrected to 60%. IFA is absent.

Glass and Pitchumoni⁵ added type AB (both antrum and body mucosa involved) and divided in Type AB –ve (PCA absent) and Type AB +ve (PCA present) in addition to type A and B.

Correa⁶ divided CG into the autoimmune, environmental and hypersecretory types; the last also known as antral gastritis is seen in patients with duodenal ulcer (DU). Correa⁷ reclassified CG on aetiological and morphological basis. The morphological classification included the atrophic and non-atrophic forms;

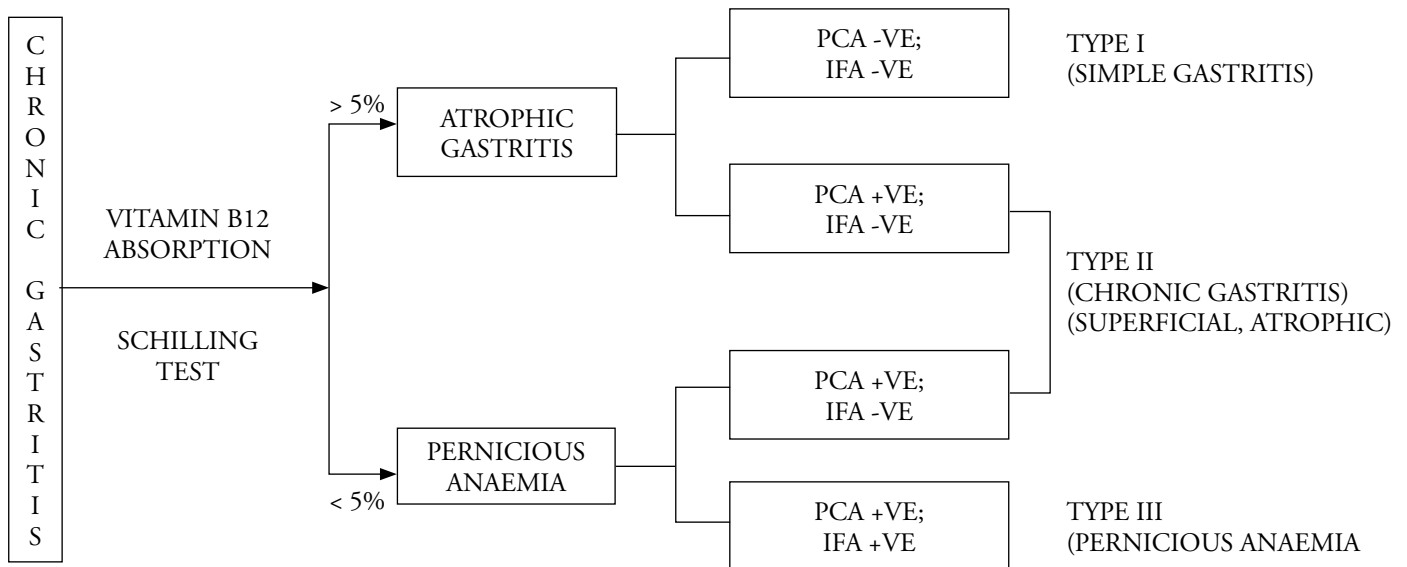


Fig. 1: The new classification of chronic gastritis

further subdivided into superficial, diffuse antral, diffuse corporal and multifocal atrophic. Multifocal atrophic gastritis is associated with intestinal metaplasia and gastric carcinoma.

Siurala et al⁸ classified CG based on its progress. CG was graded as:

Score 0: normal mucosa with no increase in infiltrating cell or loss of glands

Score 1: superficial gastritis; round cell infiltration and no loss of glands

Score 2: atrophic gastritis with slight loss of glands

Score 3: atrophic gastritis with moderate loss of glands

Score 4: atrophic gastritis with severe loss of glands

The working party on gastritis at the Sydney World Congress⁹ described a new classification based on endoscopic and histological observations. The histological findings are suffixed by the morphological characteristics and prefixed by the aetiology. The endoscopic observations show a poor correlation with histology and hence a classification based on these two parameters is inadequate.

In conclusion, the classification of CG, without including immunological criteria will be invariably inaccurate and will not help us in further understanding of this common condition.¹⁰ The classification of diseases such as acute and chronic hepatitis, glomerulonephritis, arthritis, thyroiditis are all based on immunological basis and has enabled accurate division and understanding of the aetiopathogenesis of these diseases.

DIFFERENT TYPES OF CHRONIC GASTRITIS

It is discussed as (a) *Helicobacter pylori* (HP) associated (b) Autoimmune (c) Granulomatous (d) Eosinophilic (e) Lymphocytic (f) Reflux (g) Corrosive.

Helicobacter pylori associated gastritis

The major breakthrough in our understanding of CG followed the discovery of HP in gastric mucosa by Warren and Marshall in 1983.¹¹ HP is a Gram-negative, microaerophilic, spiral organism

with flagella at one end. It is transmitted chiefly by faecal route at young age in developing countries and by person to person contact in adults in developed countries.¹² HP causes CG and persists for several decades in the gastric mucosa. CG due to HP may progress from superficial to atrophic gastritis, intestinal metaplasia and gastric carcinoma. HP is responsible for more than 80% of CG in humans.

Intestinal metaplasia can be (a) complete (Type I) in which goblet cells contain acidic mucin. Paneth cells may be present at the gland base, (b) incomplete (Type II) in which goblet cells contain acidic sialomucin (stain blue with Alcine blue), and (c) incomplete (Type III) in which goblet cells contain sulfomucin (stain brown with Alcine blue); it is especially linked with the risk of gastric carcinoma.

Pathogenesis

Hp colonizes gastric mucosa because of its motility with flagella, capacity to produce abundant urease to produce ammonia, special affinity to adhere to gastric epithelium (tissue tropism) and its ability to cause transient achlor or hypochlorhydria, on initial exposure to gastric mucosa. HP initially causes antral gastritis which may spread to varying extent in different individuals, to cause corpus gastritis of different extent and severity.

For tissue injury, at least two important cytotoxins are blamed: (i) Vacuolating cytotoxin (Vac A), and (ii) Cytotoxin-associated antigen A (Cag A).

Vac A gene is present in all HP strains but only 50% of these strains express toxin. Three signal sequence types s_{1a}, s_{1b}, s₂ and two midregion types: m₁, m₂ are described. Any combination of signal sequence and midregion except s₂/m₁ exists. Strains with s₂/m₂ genotype do not produce toxin. Vac A m₁ are more toxigenic than m₂ alleles. Strains s_{1a}/m₁ are more toxigenic than those with s_{1b}/m₁ alleles. Vac A toxin has not been specifically linked with virulence or any particular disease.¹³

Cag A⁺ strains are more toxigenic than Cag A⁻. Cag A⁺ strains usually have VAC A s_{1a} or s_{1b} genotype and are often toxigenic. In Western countries, Cag A antibodies in serum are found more

frequently in patients with DU and adenocarcinoma.¹⁴ Since vast majority (more than 90%) of Hp strains in Asia (India, China, Japan) are Cag A⁺ such correlation is not observed in them.

Immunology

Immunological events occurring in Hp associated CG, perhaps determine the progress and predominant localization (antrum or body) of the disease. PCA are produced against parietal cell cytoplasm and the specific antigen identified is the alpha and beta subunits of the gastric H⁺K⁺ ATPase (proton pump).¹⁵ The presence of PCA indicates CG and its absence does not exclude CG. In Western countries, the incidence of PCA (first detected in 1962) in serum is 20% with iron deficiency anaemia (IDA), 25% with diabetes mellitus (DM), 30% with thyrotoxicosis, 35% with Addison's disease, 60% with CG and 95% with PA patients. In patients from Mumbai, the incidence of PCA in these diseases was comparable to that reported in patients from Western countries.^{16, 17}

IFA (first detected in 1962) is against intrinsic factor (IF) secreted by parietal cells. IFA are of two types: Type I: Blocking antibodies which block the union of IF to vitamin B₁₂, and Type II: Binding antibodies which interfere with binding of vitamin B₁₂ - IF complex to ileal receptors.¹⁸

In serum, Type II IFA is found only in patients showing Type I IFA. In gastric juice, the incidence of Type II antibody is greater than that of Type I; and its detection at times is possible only after its dissociation from the small amount of IF present in gastric juice.¹⁹

In Western countries, the incidence of IFA in serum of patients with PA, thyrotoxicosis, DM, IDA, was 75%, 7%, 5%, 2%, respectively; the rarity of IFA in patients with these diseases from Mumbai was emphasised.^{16, 20} The first case report from Asia showing IFA in serum was from Mumbai.²¹ The development of IFA is independent of the sex, age, duration of disease, degree of atrophic gastritis or titer of PCA and is determined by hereditary factors. In Western countries, the incidence of IFA in relatives of patients with PA is higher than in control population.^{22, 23}

Helicobacter pylori antibodies:

Hp infection causes CG and IgA, IgG Hp antibodies (HpA) in serum indicate present or past Hp infection. Detection of these antibodies is useful for epidemiological surveys; to assess the prevalence of Hp exposure, at different age groups in the population. Hp exposure occurs in 50% of population at 5 years in developing countries and at 50 years in developed countries.^{12, 24} Early exposure in developing countries is related to poor sanitation and hygiene.

HpA crossreact with gastric autoantigens such as alpha and beta subunits of proton pump and determine the localization of the CG (body-antrum) and explains the pathogenic link between Hp and CG.²⁵

Helicobacter pylori and Pernicious Anaemia

In western countries, 50% of healthy control subjects with a positive HPA in serum showed a negative ¹³C-urea breath test, indicating absence of present infection, due to spontaneous clearance of HP from gastric mucosa.²⁶ In patients with chronic atrophic gastritis(CAG), the difference of positive serum HPA

and negative tissue staining for Hp is even more marked.²⁷ In patients with PA, a very low prevalence of Hp in the gastric mucosa (lower than in control population) and a high incidence of serum HpA is reported.^{28, 29} This indicates that among patients with severe CAG due to Hp, vast majority of them cleared the Hp over a few decades, as intestinal metaplasia makes the environment inhospitable for Hp to survive. Furthermore, as superficial gastritis progressed to CAG in the body mucosa, superficial gastritis regressed in antrum, an important observation to understand the localization of gastric mucosal damage to body mucosa in PA.³⁰

The differentiation of PA from severe CAG with HFA and vitamin B₁₂ malabsorption is solely determined on the basis of the degree of vitamin B₁₂ malabsorption. On Schilling test, less than 5% excretion in urine is diagnosed as PA and >5% as CAG. In patients with CG, Schilling test is not reproducible as the test is performed in a fasting state (without any stimulus).³¹

Granulomatous gastritis is extremely uncommon and is diagnosed in presence of granuloma in mucosal biopsies. Granuloma may be observed with Crohn's disease, sarcoidosis, tuberculosis, histoplasmosis, syphilis and suture material (postoperative).

Eosinophilic gastritis is believed to be an allergic manifestation characterized by eosinophilic infiltration of gastric mucosa, with or without peripheral eosinophilia. Antral infiltration is common and may even cause an ulcer or a granuloma.³² Parasitic infection should be excluded.

Lymphocytic gastritis is indicated by presence of lymphocytes in surface epithelium and mucosa and predominantly affects the body mucosa.

Reflux gastritis is due to reflux of duodenal contents (especially bile) in gastric lumen, usually following operations on stomach (gastrojejunostomy or partial gastrectomy).

Symptomatology

The vast majority of chronic gastritis patients are asymptomatic. Presence of non-colicky pain in upper abdomen, occurring daily, within 15 minutes after ingestion of a spicy meal (normal Indian diet), and absence of pain on delay or omission of a spicy meal, raises suspicion of CG.³³ Heaviness in abdomen after a meal is not an uncommon manifestation. PA patients may present with anaemia or neurological abnormalities (subacute combined degeneration).³⁴

Investigations

The diagnosis of CG can be confirmed by gastric mucosal biopsy. Endoscopic observations alone are not sufficient to diagnose CG; at least two biopsies should be obtained from body and antrum each. Presence of lymphoid follicles and / or polymorphonuclear leucocyte infiltration is highly suggestive of Hp infection. Hp can be identified near surface epithelium with routine HE stain and with greater accuracy with special stains (modified Giemsa, Warthin-starry, Genta).

Hp can also be detected by rapid urease test (rarely false-negative); abundant urease in Hp converts urea to ammonia and pH change is appreciated on colour change from yellow to red with phenol red. Hp is a difficult organism to grow in culture and may take more than 3 days. Culture is essential to assess susceptibility to different antibiotics.

The non-invasive test, HpA in serum, indicates past or present infection.³⁵ Use of serology as a screening test for selecting young dyspeptic patients for endoscopy is practiced in a few centres. The other non-invasive test for detection of Hp is urea breath test (UBT). Following an oral meal containing ¹⁴C-urea, ¹⁴CO₂ liberated is absorbed and exhaled in breath and this is measured with liquid scintillation. The test should not be performed in pregnant women and children. ¹³C-urea (isotope) is measured with mass spectrometry.³⁶ UBT test is useful to diagnose presence of infection and can provide some useful information to assess density of Hp in whole of gastric mucosa.

The faecal antigen test (FAT) utilizes HpA adsorbed to microwells. The sensitivity and specificity of this test is more than 90% and detects presence of infection. For confirming eradication of Hp after treatment, UBT or FAT should be performed four weeks after completion of treatment; the former is marginally more accurate.³⁷

PCA in serum indicates presence of CG even in healthy control subjects. IFA in serum is diagnostic for PA.^{3,23}

Gastric Secretion in Chronic gastritis

HFA is always present with PA and can also occur with severe CAG.²³ In patients with CG, acid secretion may be normal, hypochlorhydria or even increased with antral gastritis (e.g. DU) and a good correlation between histology and acid secretion was reported.^{38,39} Serum gastrin level may be markedly raised in PA due to loss of normal acid inhibition of G cells in antrum.³

IF is markedly reduced (<200 units / hr) in PA and is normal or reduced with CAG. When IF is markedly reduced, vitamin B₁₂ malabsorption is observed.^{3,31}

Vitamin B₁₂ Absorption

In PA and in some patients of CG with HFA, vitamin B₁₂ absorption is impaired, as IF secretion is markedly reduced.⁴⁰ In normal subjects, mean IF secretion in stomach in basal state is 2600 and 1300 units per hr in men and women, respectively; this is far greater than the minimal amounts of 500 units of IF required for absorption of 1µg of vitamin B₁₂. In some patients with CG, the IF content of gastric juice may be subnormal and inadequate for vitamin B₁₂ absorption in a fasting state but subnormal and yet sufficient for this purpose in a stimulated state. Hence vitamin B₁₂ absorption test was recommended after ingestion of coffee (without milk).³¹

In stomach, vitamin B₁₂ can attach to either IF or R-protein; the preference for attachment to R-protein is far greater than that with IF. Vitamin B₁₂-R-protein complex is cleaved by pancreatic enzyme in upper small intestine and free vitamin B₁₂ now combines with IF and IF-B₁₂ complex attaches to ileal receptors for its absorption. Vitamin B₁₂ malabsorption hence could result from very low IF secretion in stomach (PA or CAG) or failure of IF-B₁₂ complex to be absorbed due to ileal disease, resection or bypass or due to failure of vitamin B₁₂-R-protein to cleave because of severe pancreatic enzyme deficiency. In PA, a repeat Schilling test with exogenous IF, corrects vitamin B₁₂ malabsorption.

Prognosis

Chronic superficial gastritis usually progresses to CAG, intestinal metaplasia, dysplasia and occasionally to adenocarcinoma, over

several decades. WHO has classified Hp as a class I carcinogen, though the risk of carcinoma is only marginally higher than in control population. Neither eradication of Hp nor surveillance of patients of CG or PA for early detection of carcinoma is recommended, as the risk is minimal after several decades and it is not cost-effective.

Treatment

Hp eradication from gastric mucosa is recommended only in patients with peptic ulcer and mucosa-associated lymphoid tissue (MALT) lymphoma. In patients with CG, Hp eradication is not recommended as the disease is asymptomatic, progresses very slowly over several decades, multiple antibiotic treatment has significant side-effects and eradication of Hp in a large population may not be always beneficial. With excellent sanitation in Western countries, the lack of exposure of gastric mucosa to Hp, has increased the risk of Barrett's oesophagus and columnar cell adenocarcinoma at cardioesophageal junction⁴¹ and the beneficial role of Hp needs to be recognised.

For PA, vitamin B₁₂ injection 500 µg once a week for 8 weeks, followed by once every 3 months for lifetime is recommended. For eosinophilic gastritis, steroid therapy is useful.

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