Update Article

Helicobacter pylori Link to Pernicious Anaemia

HG Desai*, PA Gupte**

Abstract

An immunological classification of chronic gastritis based on the detection of Helicobacter pylori (H. pylori) antibody, parietal cell antibody, intrinsic factor antibody, is reported. H. pylori chronic gastritis, slowly progresses to atrophic gastritis, in the majority of patients; in a few patients, with genetic susceptibility to form intrinsic factor antibody, it progresses to pernicious anaemia. In majority of patients of pernicious anaemia, H. pylori gradually disappears from the gastric mucosa, on development of intestinal metaplasia in them. Atrophic gastritis results from H. pylori or non H. pylori. H. pylori infection is diagnosed in the presence of H. pylori in the gastric mucosal biopsy and/or H. pylori antibody (IgG) in the serum. The presence of the genetic factor (intrinsic factor antibody) is essential for the diagnosis of pernicious aneamia. Pernicious anaemia patients without intrinsic factor antibody, should be correctly diagnosed as atrophic gastritis, in view of the absence of the genetic factor (intrinsic factor antibody) in them. ©

Introduction

Diseases such as acute or chronic hepatitis, thyroiditis, glomerulonephritis, arthritis are all classified on the basis of immunological parameters. A significant progress in the classification of chronic gastritis will be achieved only when immunological parameters are given maximum importance (Fig. 1).

The immunological classification of chronic gastritis was independently reported from India (March 1973) [1] and Australia (May 1973).[2] It was based on the presence of parietal cell antibody (PCA: 1962)[3] and intrinsic factor antibody (IFA: 1963)[4] in the serum of patients of pernicious anaemia (autoimmune : Type A). Following the discovery of Helicobacter pylori (H. pylori) in endoscopic gastric mucosal biopsy of humans in 1983,[5] the etiological agent in 80% of patients of chronic gastritis is H. pylori, was reported.[6,7] An immunological classification based on H. pylori antibody (HPA:1986),[8] PCA, IFA, to identify the environmental factor " H. pylori (or non H. pylori) and the genetic factor – IFA, is reported.

Immunological classification

Chronic gastritis should be divided in two groups (i) H. pylori induced (ii) non-H. pylori. The causes of non-H. pylori chronic gastritis are – eosinophilic, lymphocytic, granulomatous, reflux (post-operative), post-radiation, corrosive; they are not discussed, as typical gastric mucosal histology and history, establishes the diagnosis. The chronic gastritis (acquired) in a patient with a genetic susceptibility to form IFA.[9] progresses to pernicious anaemia.[9]

*Director Gastroenterology; **Hon Gastroenterologist; Jaslok Hospital and Research Centre, Dr. G Deshmukh Marg, Mumbai – 400 026, India.
Received : 22.6.2007; Revised : 24.9.2007;
Re-Revised : 10.10.2007; Accepted : 29.10.2007

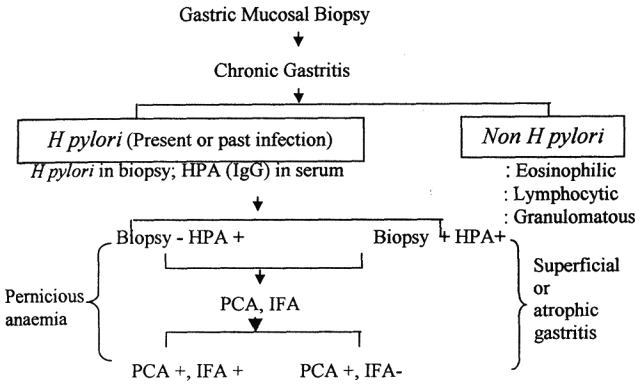

Fig 1: Algorithm for the diagnosis of pernicious anaemia
H pylori : Helicobacter pylori; HPA : Helicobacter pylori antibody
PCA : Parietal cell antibody; IFA : Intrinsic factor antibody

Helicobacter pylori and immunology

HPA – IgA, IgG indicates present and past infection respectively.[10] HPA cross react with gastric autoantigens such as the alpha and beta subunits of proton pump and determines the progress and localization (body or antrum) of gastric mucosal damage.[11]

PCA are formed against the parietal cell cytoplasm and the specific antigen identified is the alpha and beta units of the gastric H^+K^+ATPase (proton pump).[12] A positive correlation between HPA and PCA was observed in patients of pernicious anaemia; these antibodies recognize different epitopes on H^+K^+ATPase.[13]

Intrinsic factor antibody

IFA is against the amino acid sequence 251 – 256 of intrinsic factor, secreted by the parietal cells.[14] The

Table 1 : Intrinsic factor antibody (genetic factor) determines the division of pernicious anaemia and atrophic gastritis (with HFA and vitamin B_{12} malabsorption)

Diagnosis	Atrophic Gastritis	Pernicious Anaemia
Augmented histamine test		
: Acid output	Hypochlorhydria or HFA	HFA
: Intrinsic factor	> 200 units/hr	< 200 units/hr
^{58} Co vitamin B_{12} excretion	5 - 10 % (or <5%)*	< 5 %
Serum gastrin	< 200 ng/l	> 200 ng/l
Serum pepsinogen I	> 30 ug/l	< 30 µg/l
Serum pepsinogen I : II ratio	> 3	< 3
Immunology:	HPA +, PCA +	HPA +, PCA +
	IFA –	IFA +
Etiology: Acquired	H pylori (or non H. pylori)	H pylori (or non H. pylori)
Genetic factor	Absent	Present

HFA: Histamine fast achlorhydria; *reference(22); H pylori: Helicobacter pylori; HPA: Helicobacter pylori antibody; PCA: Parietal cell antibody; IFA: Intrinsic factor antibody

Blocking (type I) and Binding (type II) IFA are present in the serum and/or gastric juice of patients of pernicious anaemia.[15-17] Initially Type II antibodies were considered rare[5] but subsequently a high incidence of type II antibody in sera of patients of pernicious anaemia was reported.[18] Estimation of total (type I and II) antibodies with enzyme linked immunosorbent assay (ELISA) is recommended.[18] The prevalence of IFA in serum of patients of pernicious anaemia increased significantly during a follow up of 70 (14-137) months.[19] The incidence of IFA in first – degree relatives of patients of pernicious anaemia was as high as 22%.[20] Amongst 16 Indian patients of atrophic gastritis with histamine fast achlorhydria (HFA) with severe vitamin B_{12} malabsorption (< 5% excretion on Schilling test), IFA was present in only 2, indicating the rarity of IFA in Indian patients, due to a genetic factor.[21-23] The development of IFA is independent of the sex, age, duration of disease, degree of atrophic gastritis or titre of PCA and is determined by a genetic factor.[24]

Discussion

Is there any link between H. pylori infection and pernicious anaemia?

Fifty percent of healthy control subjects with a positive HPA in serum showed a negative urea breath test, indicating absence of H. pylori (at present) in the gastric mucosa.[6] In patients with atrophic gastritis, the difference of a positive serum HPA and a negative staining for H. pylori, is even more marked.[25,26]

In pernicious anaemia patients, the prevalence of H. pylori in the gastric mucosal biopsy is low;[27-30] it was 11% (71% in controls),[31] 21% (39% in controls),[32] and 40%[33] and was related to the development of intestinal metaplasia in them.[29,30,34] In contrast, the prevalence of HPA in serum of pernicious anaemia patients was 57% (in patients > 60 years),[35] indicating past exposure to H. pylori infection. In 30 patients of pernicious anaemia, the prevalence of HPA and PCA was 83% and 100% respectively.[13] The first – degree relates of pernicious anaemia and duodenal ulcer patients, showed a comparable prevalence of H. pylori in the gastric mucosal biopsy in young relatives but a markedly decreased prevalence H. pylori in the older age group relatives of pernicious anaemia patients. This observation indicates the role of H. pylori in the early stage of pernicious anaemia.[36]

The immunological classification (HPA, PCA, IFA) of chronic gastritis is based on two questions: (i) whether H. pylori infection (present or past) is responsible for the atrophic gastritis? (ii) whether a genetic factor, indicated by IFA formation, has any contribution? The environmental and genetic factor earlier blamed for pernicious anaemia[9] are now recognized as H. pylori (or non H. pylori) and IFA formation respectively.[21,22,36,37]

The presence of H. pylori in the gastric mucosa and / or HPA (IgG) in serum indicates H. pylori, as the aetiological agent of atrophic gastritis (acquired). The patients of atrophic gastritis with histamine fast achlorhydria, severe vitamin B_{12} malabsorption (<5% excretion on Schilling test) without IFA in serum, should not be labelled as pernicious anaemia.[22] The presence of IFA (genetic factor) should be considered essential for the precise diagnosis of pernicious anaemia and its absence should exclude it.[22,37,38]

Clinical importance

In a patient with provisional diagnosis of pernicious anaemia, (macrocytic anaemia with low serum vitamin B_{12}), the next investigation should be serum IFA. Investigations shown in Table 1 (except immunological) are optional.[39-42] The enormous cost saving in the diagnosis of pernicious anaemia is obvious.

Conclusions

H. pylori link to pernicious anaemia is emphasised. The immunological parameters (HPA, PCA, IFA) should be given maximum importance in the separation of patients of atrophic gastritis with HFA and poor Vitamin B12 malabsorption from those of pernicious anemia. The presence of IFA should be considered diagnostic of pernicious anaemia and its absence should exclude it.

References

1. Desai HG, Antia FP. A second look at chronic gastritis. A new classification. Indian J Med Sci 1973;27:217-24.

2. Strickland RG, Mackay IR. A reappraisal of the nature and significant of chronic atrophic gastritis. Am J Dig Dis 1973;18:426-40.
3. Taylor KB, Roitt IM, Doniach D, et al. Autoimmune phenomena in pernicious anaemia: gastric antibodies. Br Med J 1962;2:1347-52.
4. Ardeman S, Chanarin PI. A method for the assay of human gastric intrinsic factor and for the detection and titration of antibodies against intrinsic factor. Lancet 1963;2:1350-4.
5. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;I:1273-5.
6. Meyer B, Werth B, Beglinger C, et al. Helicobacter pylori infection in healthy people: a dynamic process? Gut 1991;32:347-50.
7. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med 2002;347:1175-86.
8. Jones DM, Eldridge J, Fox AJ, et al. Antibody to the gastric Campylobacter-like organism ("Campylobacter pyloridis") – clinical correlations and distribution in the normal population. J Med Microbiol 1986;22:57-62.
9. Whittington S, Mackay IR. Ungar B, et al. The genetic factor in pernicious anaemia. A family study in patients with gastritis. Lancet 1969;1:951-4.
10. Perez-Perez GI, Sworkin BM, Chodos JE, et al. Campylobacter antibodies in humans. Ann Intern Med 1988;109:11-7.
11. Negrini R, Lisato L, Zanelli I, et al. Helicobacter pylori infection induces antibodies cross-reacting with human gastric mucosa. Gastroenterology 1991;101:437-45.
12. Jones CM, Callaghan JM, Gleason PA, et al. The parietal cell autoantibodies recognized in neonatal thymectomy-induced murine gastritis are the alpha and beta subunits of the gastric proton pump. Gastroenterology 1991;101:287-94.
13. Ma JY, Borch K, Sjostrand SE, et al. Positive correlation between H, K-adenosine triphosphatase autoantibodies and Helicobacter pylori antibodies in patients with pernicious anaemia. Scan J Gastroenterol 1994;29:961-5.
14. Gueart JL, Safi A, Aimone-Gastin I, et al. Autoantibodies in pernicious anaemia type I patients recognize sequence 251-256 in human intrinsic factor. Proc Assoc Am Physicians 1997;109:462-9.
15. Samloff IM, Kleinman MS, Turner MD, et al. Blocking and binding antibodies to intrinsic factor and parietal cell antibody in pernicious anaemia. Gastroenterology 1968;55:575-83.
16. Schade SG, Feick PB, Muckerheide BS, et al. Occurrence in gastric juice of antibody to a complex of intrinsic factor and vitamin B_{12}. N Engl J Med 1966;275:528-31.
17. Shackelton PJ, Fish DI, Dawson DW. Intrinsic factor antibody tests. J Clin Pathoil 1989;42:210-2.
18. Waters HM, Dawsson DW, Howarth JE, Geary CG. High incidence of type II autoantibodies in pernicious anaemia. J Clin Pathol 1993;46:45-7.
19. Davidson RJL, Atrah HI, Sewell HF. Longitudinal study of circulating gastric antibodies in pernicious anaemia. J Clin Pathol 1989;42:1092-5.
20. Roitt IM, Doniach D, Shapland C. Autoimmunity in pernicious anaemia and atrophic gastritis. Ann New York Acad Sci 1965;124:644-56.
21. Varis K, Ihanani T, Harkonen M, Samloff IM, Siurala M. Gastric morphology, function and immunology in first-degree relatives of probands with pernicious anaemia and controls. Scand J Gastroenterol 1979;14:129-39.
22. Desai HG, Antia FP. Vitamin B_{12} malabsorption due to intrinsic factor deficiency in Indian subjects. Blood 1972; 40:747-53.
23. Desai HG, Borkar AV, Dighe PK. Parietal cell and intrinsic factor antibodies in Indian subjects. Scand J Gastroenterology 1968; 3:321-6.
24. Desai HG, Borkar AV, Dighe PK, et al. Pernicious anaemia and thyrotoxicosis in an Indian subject. Gastroenterology 1968;54:940-4.
25. Karnes WE, Samloff IM, Siurala M, et al. Positive serum antibody and negative tissue staining for Helicobacter pylori in subjects with atrophic body gastritis. Gastroenterology 1991;101:167-74.
26. Annibale B, Negrini R, Caruana P, et al. Two-thirds of atrophic body gastritis patients have evidence of Helicobacter pylori infection. Helicobacter 2001;6:225-33.
27. Flejou IF, Bahame P, Smith AC, et al. Pernicious anaemia and campylobacter like organism; Is the gastric antrum resistant to colonization? Gut 1989;30:60-4.
28. Oconner HJ, Axon ATR, Doxon MF. Campylobacter like organisms unuasal in Type A (pernicious anaemia) gastritis. Lancet 1984;1:57.
29. Juan DG, Sancho FJ, Sainz S, et al. Campylobacter pylori and pernicious anaemia. Lancet 1988;1:57.
30. Meyrick TJ. Campylobacter-like organisms in gastritis. Lancet 1984;2:1217.
31. Fong TL, Dooley CP, Dehesa M, et al. Helicobacter pylori infection in pernicious anaemia: a prospective controlled study. Gastroenterology 1991;101:328-32.
32. Presotto F, Sabini B, Cecchetto A, et al. Helicobacter pylori infection and gastric autoimmune diseases: is there a link? Helicobacter 2003;8:578-84.
33. Sari R, Ozen S, Aydogdu I, et al. The pathological examination of gastric mucosa in patients with Helicobacter pylori – positive and – negative pernicious anaemia. Helicobacter 2000;5:215-21.
34. Genta RM, Graham DY. Intestinal metaplasia, not atrophy or achlorhydria creates a hostile environment for Helicobacter pylori. Scand J Gastroenterol 1993;28:924-8.
35. Faisal MA, Russell RM, Samloff IM, et al. Helicobacter pylori infection and atrophic gastritis in the elderly. Gastroenterology 1990;99:1543-4.
36. Varis O, Valle J, Siurala M. Is Helicobacter pylori involved in the pathogenesis of the gastritis characteristic of pernicious anaemia? Comparison between Pernicious anaemia relatives and duodenal ulcer relatives. Scand J Gastroenterol 1993;28:705-8.
37. Ungar B, Whittingham S, Francis CM. Pernicious anaemia incidence and significance of circulating antibodies to intrinsic factor and to parietal cells. Aust Ann Med 1967;16:226-9.
38. Desai HG. Investigations proposed to accurately classify chronic gastritis. J Assoc Physicians India 2007;55:292-6.
39. Carmel R. Pepsinogens and other serum markers in pernicious anaemia. Am J Clin Pathol 1988;90:442-5.
40. Kay AW. Effect of large doses of histamine on gastric section of Hcl – an augmented histamine test. Brit Med J 1953;2:7780.
41. Mollin DL, Booth CC, Baker SJ. The absorption of vitamin B_{12} in control subjects, in addisonian pernicious anaemia and in the malabsorption syndrome. Br J Haematol 1957;3: 412-28.
42. Desai HG, Zaveri MP, Antia FP. Increased vitamin B_{12} absorption after ingestion of coffee. Gastroenterology 1973;65:694-5.