CHAPTER

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Emergence of Celiac Disease and Crohn's Disease in India

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Introduction

With improved economy, living conditions and personal hygiene there has been a distinct decline in occurrence of infectious diseases like cholera, amebic dysentery and bacillary dysentery in this country. At the same time however, changes in life style and food habits have resulted in a rise in the incidence of diseases like ischemic heart disease, diabetes mellitus, and obesity. Among gastrointestinal disorders, two diseases namely celiac disease and Crohn's disease have certainly emerged as fairly common diseases in India during the last one decade.

Celiac Disease

The causes of chronic diarrhea and malabsorption in India have been traditionally recognised to be tropical sprue, parasitic and bacterial infections, and intestinal tuberculosis.[1] Only an occasional patient would be diagnosed to have malabsorption due to celiac disease. Among patients with malabsorption, tropical sprue has been the focus of investigation by Indian clinicals and researchers.[1-2] Because of much similarity in the histopathological pictures of celiac disease and conditions like tropical sprue, parasitic infestations and small intestinal bacterial overgrowth and lack of a pathognomonic feature of celiac disease perhaps many patients with the latter disease remained unrecognised and got wrongly labeled as 'tropical sprue ' or idiopathic malabsorption. Research in the field of celiac disease thus remained neglected in India till recently.[2-5]

Many misconceptions about celiac disease prevail e.g. 1) it is a disease of children, 2) it is a disease of European nations and is uncommon in our part of the world, and 3) involvement of the intestine is a must for the diagnosis of celiac disease. Generally, celiac disease has been recognized by pediatricians only. There has thus been an impression and a wide belief that celiac disease is a disease of children and does not occur in adults ignoring the very fact that all these children will grow in adults. Also, those children with celiac disease in whom diagnosis was either missed or remained misdiagnosed, would present in adulthood with either typical or atypical manifestations to endocrinologists with short stature, to hematologists with anemia, to orthopedicians with metabolic bone disease or to dentists with dental enamel defects.[6-10]

Celiac disease affects about 1% of the general population world over.[11-12] The highest reported prevalence is in the Western European countries and in those countries where Europeans had emigrated, notably North America and Australia. The reported prevalence of celiac disease in these countries varies from 100 to 300 per 100,000 population. Until recently, celiac disease was considered

uncommon in the United States, with an estimated prevalence of 1 per 3,000 population. However, greater awareness of its varied presentations and the availability of new, accurate serologic tests have led to the recognition that celiac disease is relatively common, affecting 1 of every 120 to 300 persons in North America.[13] With increase in awareness and wider applicability of serological tests, celiac disease is now being reported from most parts of the world. However, reports of celiac disease from Asia have been scarce. The symptoms are diverse, and the disease may be symptom free; it is therefore apparent that, without active serologic screening, the majority of patients with celiac disease will remain undiagnosed in the future.

The epidemiological changes of celiac disease can be efficiently conceptualized by the iceberg model.[14-15] The prevalence of celiac disease can be conceived as the overall size of the iceberg, which is primarily influenced by the frequency of the predisposing genotypes in the population. Indeed, celiac disease seems to be more common wherever the frequency of the HLA-DR3 (and DQ2) is high, such as in Europe, the United States, and North Africa. The dimension of this iceberg also depends, to a lesser extent, on disease definition, i.e., whether subjects with so-called latent or potential celiac disease or those with mild enteropathy are "counted" as affected individuals. In countries where a substantial part of the population is of European origin, the prevalence of celiac disease is likely to be more stable than previously thought, roughly in the range of 0.5%–1% of the general population. A sizable number of these cases are properly diagnosed because of suggestive complaints (e.g., chronic diarrhea, unexplained iron deficiency) or other reasons (e.g., family history of CD). These cases make up the visible part of the celiac iceberg. However, as previously reported, screening studies show that for each diagnosed case of celiac disease an average of 5–10 cases remain undiagnosed (the submerged part of the iceberg).[14-15] The "water line," namely the ratio of diagnosed to undiagnosed cases, depends on several factors: (1) awareness of celiac disease: "think of CD and you will find it" is an aphorism worth remembering; differing awareness, and consequently variable thresholds for serologic celiac disease testing, is likely to explain a substantial part of the wide differences in incidence between countries; (2) availability of diagnostic facilities: lack of both laboratory equipment and personnel trained in celiac disease diagnosis is a major problem in large areas of the world, e.g., North Africa, the Middle East, and India, where the frequency of celiac disease is currently underestimated; (3) and variations in clinical intensity: at both individual and population levels.

Lal et al[16] have recently conducted a sero-prevalence study in healthy school children in Chandigarh and contrary to popular belief reported the prevalence of celiac disease to be 1: 120 in them, which is almost equal to that in Europe and North America. There are scarce reports of sero-prevalence of celiac disease from other parts of India. We do appreciate that there may be a geographical variation in the prevalence of celiac disease in different parts of India. And yet if we apply this prevalence data to the population of India (1100 million), the expected number of patients with celiac disease in India may be huge i.e. 8.8 million.

The gluten sensitivity which has been regarded principally as a disease of the small intestine is a historical misconception. Marsh's modern definition of celiac disease that it is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals is more appropriate." Such responsiveness may also find expression of gluten sensitivity in organs other than intestine.[17-18] This definition implies that gluten sensitivity may solely be manifested in the skin (dermatitis herpetiformis), liver (asymptomatic increase in transaminases) and nervous system (seizure, peripheral neuropathy) without involvement of intestine.[14,18-20] The absence of an enteropathy in such a specialized situation should not preclude a diagnosis of celiac disease and treatment of such patients with gluten-free diet should not be denied.

Table 1 : When to suspect celiac disease

Chronic diarrhea (small intestinal type)
Chronic anemia, resistant to iron therapy
Growth failure
Short stature
Metabolic bone disease

Gastroenterologists, hepatologists, endocrinologists, gynecologists, neurologists, dermatologists and other physicians need to be aware of these developments, if the diagnosis and treatment of the diverse manifestations of gluten sensitivity are to be advanced (Table 1).

The rarity of celiac disease in India may not be real. A low index of suspicion and reliance on classic symptoms may be resulting in significant underdiagnosis of celiac disease in India. Sood at al[21] from Ludhiana reported a rising incidence of celiac disease in their hospitalized patients with celiac disease over last 10 years. They argued that this increased incidence is either due to increased awareness of the disease or a change in the type of wheat we produced and consumed. The former appears more true to me as incidence of a genetic disease will not increase over such a short period of time in the same geographical region. In recent years, celiac disease is recognized much more frequently in India not only in children but also in adults.[1,2,4,20,21]

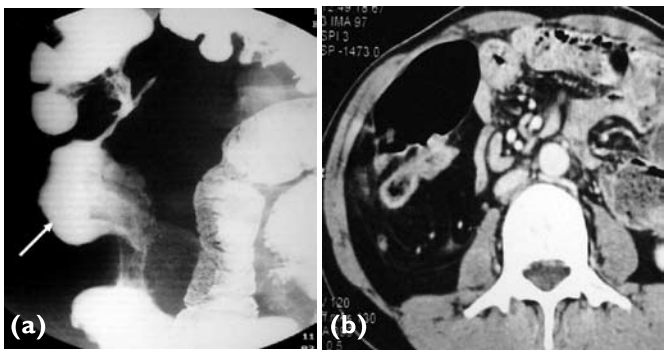
Rising incidence and prevalence of Crohn's disease in India

Many recent reports have highlighted the rising prevalence and incidence of inflammatory disease (IBD) in Asia.[22-24] Although ulcerative colitis (UC) is reported more commonly, Crohn's disease is also being recognized and reported quite frequently from Asia in recent years.[24] In the developing countries, amebic colitis and intestinal tuberculosis pose the greatest difficulty in differentiating them from ulcerative colitis and Crohn's disease, respectively. The clinical, endoscopic, histological and radiological features of Crohn's disease are indeed quite similar to those of intestinal tuberculosis. (Table 2) (Fig. 1, 2) Features such as deep linear ulcerations, aphthous ulcerations, perianal disease, and non-caseating granuloma are however, quite unique to Crohn's disease.[25-28] On the other hand, epicenter of the disease being ileocecal area, lack of bleeding per rectum and caseating grannuloma are distinguishing features of intestinal tuberculosis. We recently observed that blood in the stool, malabsorption, peri-anal involvement and lack of intestinal obstruction are predictors of CD and help differentiate it from intestinal tuberculosis.[29] The final differentiation between the

Table 2 : Differentiating features between Crohn's disease and intestinal tuberculosis

Features	Intestinal tuberculosis	Crohn's disease
Clinical features		
Duration of the disease	Shorter	Longer
Bloody diarrhea	More frequent	Less frequent
Peri-anal disease	Rare	60-80%
Intestinal colic and obstruction	60-90%	60-80%
Extra-intestinal features	Rare	Common
Endoscopic features		
Colonic and intestinal ulcers	Circumferential/ transverse	Longitudinal
Aphthous ulcers	Absent	Present
Cobblestoning	None	Characteristic
Intestinal strictures	Small	Long and multiple
Status of ileocecal valve	Narrow	Gaping
Intestinal fistula	Uncommon	More common
Radiological features		
Mesenteric fat proliferation	Absent	Characteristic
Lymph nodes	Caseation+	Non-caseating
Histological features		
Granuloma	Large, confluent and caseating	Small, discrete, loose and noncaseating

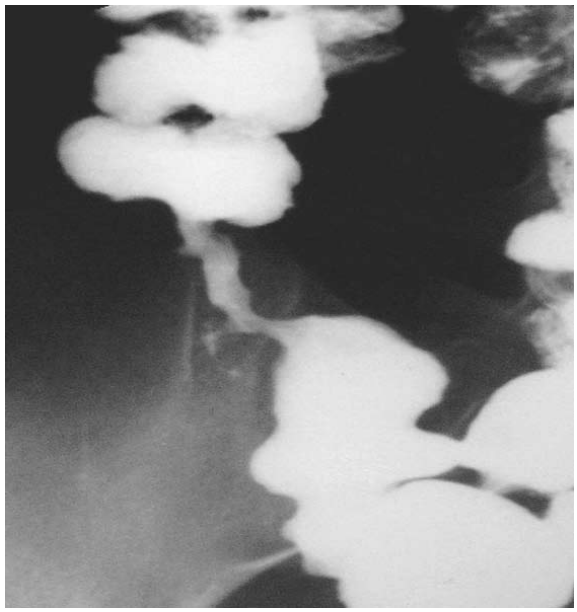
Figure 1 : Barium meal follow through study (a) showing stricture of the terminal ileum and sacculations of the anti-mesenteric border, suggestive of Crohn's disease. An axial CECT (b) showing mild uniform concentric wall thickening of the cecum with marked surrounding fibro-fatty proliferation, suggestive of Crohn's disease



two however, comes from demonstration of acid fast bacilli (*Mycobacterium tuberculosis*) in the tissue specimen. This issue may likely get complicated further if *Mycobacterium avium paratuberculosis* does become accepted as a possible cause of CD.[30] In the geographical area where the prevalence of intestinal tuberculosis is less in general population (except in immunodeficient individuals), diagnosing CD is easier. On the other hand, in those geographical areas and countries where intestinal tuberculosis is still common (India, China), making the diagnosis of CD is not easy. In a given clinical situation, if the diagnosis of CD or intestinal tuberculosis is not established, it is logical and indeed customary to put such patients on anti-tubercular treatment and see the response. If no response is observed within 6-8 weeks, a definitive diagnosis of CD is established.[24,28] However, one should remember that many patients with CD may also respond temporarily to anti-tubercular treatment. The disease reappears either early or a few months/ years later after the treatment is stopped. In many Asian countries, patients with CD are not infrequently misdiagnosed as intestinal tuberculosis.

The rising incidence and prevalence of Crohn's disease has also been observed in other Asian Countries such as Japan, HongKong, and Taiwan as is evident from the spurt of publications on

Figure 2 : Barium meal follow through study showing contracted and pulled up cecum with narrowing of the terminal ileum and gaping of the ileocecal valve, suggestive of intestinal tuberculosis



CD from these countries.[31-33] There are of course minor variations in presentation of CD in different countries. These variations may be partly because of the extent of awareness as well as the diagnostic facilities available in the specific community. Many of the evolving disease states may not be detected because of lack of suggestive symptoms and sensitive tests.

Loftus in a recent review noted that, although both incidence and prevalence rates of IBD in Asian countries were still low compared with that in Europe and North America, they were increasing rapidly.[34] He documented the emergence of UC and commented that the incidence of CD was still low but postulated that it would rise and match the incidence of UC in the same way as happened during the mid-1990s' explosion of IBD in Europe. Yang et al pointed out that the gap between areas with conventionally high and low incidence rates was diminishing, but comparisons between different Asian regions was not yet possible because of lack of reliable population data.[34]

Let us review the evolution of IBD in North America and Europe. At the very beginning, ulcerative colitis had been reported to be more common than CD. CD followed UC after a gap of approximately 60 years in these countries. The rising incidence of CD in these countries coincided with improvement in sanitation and hygiene.[34] In India and other Asian nations about 60 years later, similar trend is being observed in the emergence of UC and CD.[24,35]

If there is a real increase in the incidence of CD in Asia, what are the factors responsible for it? Inflammatory bowel disease (IBD) results from an interaction between genetic and environmental factors, leading to an abnormal immune response of the gut mucosa to intra-luminal antigens.[36] Genetic factors appear to play a more dominant role in the causation of CD than UC. However, hereditary factors do not change in a few decades and hence cannot account for the increasing incidence of CD. Some thing in our environment appears to confer a major risk of developing IBD. The prevalence of IBD varies with time, geography, socioeconomic conditions, and occupation. The incidence of IBD in North America and Europe increased dramatically during the 20th century. IBD is more common in urban than in rural areas. IBD is less common in persons who do manual labor and are exposed to dirt. It is less common in military veterans, if they were prisoners of war or had served in combat in the tropics. Similarly, it is common in highly developed industrialized countries but is rare in less developed tropical countries.[34] Furthermore, IBD emerges as countries develop. Persons belonging to populations with a low incidence of IBD, on migration to developed countries, show a higher incidence of IBD, suggesting that environmental factors are important in the pathogenesis of IBD.[34]

IBD appears to result from a dys-regulated immune response to intestinal contents. Inflammatory cells are always present in normal mucosa poised to protect us from potentially harmful luminal agents.[36,37] In patients with CD or UC, the normal tightly controlled activity of the mucosal immune system becomes excessive resulting in profound tissue damage. In most animal models of IBD, inflammation results from an excessive T helper 1 (Th1) response. Cellular immune responses often polarize into the Th1 type, characterized by cells that make IL-12, interferon gamma, or tumor necrosis factor alfa and the Th2 type, characterized by cells that make IL-4, IL-5, and IL-13. Diseases associated with polarized Th1 responses include CD, multiple sclerosis, insulin-dependent diabetes, rheumatoid arthritis, and psoriasis. Diseases associated with polarized Th2 responses include atopic dermatitis, allergic rhinitis, and asthma.[37]

The etiology of IBD is centered on the interaction of intestinal microflora with the host immune system. Chronic infections acquired in childhood induce immune tolerance to various extrinsic antigens by stimulating regulatory cells of the immune system, which have an anti-inflammatory activity. A reduction in the frequency of childhood infections has been correlated with an increase in autoimmune and allergic disorders in many epidemiological studies.[37-38] Children and adults from developing countries are often infested with helminths like Ascaris lumbricoides and hookworms.[37,-39] Helminths regulate and modulate the immune system of the host. It has been demonstrated that they modulate the immune response away from Th1 response, meaning thereby that there is depressed Th1 immune response in them. Mice harboring helminths have depressed Th1 and augmented Th2 responses to test antigens and mycobacteria. The helminths tend to accomplish this task through multiple mechanisms including release of compounds that trigger IL-10 or downregulation of IL-12 and tumor necrosis factor alfa production, release of prostaglandin E2, and TGF-B-like molecules. Elimination of helminths with better sanitation predisposes a susceptible individual to an unlimited activation of Th1 type immune response. Such an effect may explain the rising incidence of CD in developing countries.[37-39]

In conclusion, the reasons for rising incidence and prevalence of celiac disease and Crohn's disease in India and Asia may not only be due to an increase in the number of new cases but it may partly be due to recognition of its existence and proper diagnosis of this condition. We suspect that a number of adult patients with chronic diarrhea, refractory anemia, short stature, infertility, amenorrhea and metabolic bone disease have underlying celiac disease. The diagnosis of celiac disease is not considered in them because of lack of awareness and lack of diagnostic facilities. It is so important to recognize hidden cases of celiac disease in the community as a proper treatment may change substantially the quality of life of these patients. Similarly, we need to sieve out patients with Crohn's disease from a larger group who are otherwise diagnosed to have intestinal tuberculosis and even ulcerative colitis.

References

1. Ramakrishna BS. Malabsorption syndrome in India. Indian J Gastroenterol 1996;15:135-41.
2. Ranjan P, Ghoshal UC, Aggarwal R, et al. Etiological spectrum of sporadic malabsorption syndrome in northern Indian adults at a tertiary hospital. Indian J Gastroenterol. 2004 ;23:94-8.
3. Poddar U, Thapa BR, Nain CK, et al. Celiac disease in India: are they true cases of celiac disease? J Pediatr Gastroenterol Nutr 2002 ;35:508-12.
4. Makharia GK, Baba CS, Khadgawat R. Variations of presentation of celiac disease in adults. Indian J Gastroenterol 2007 (In press).
5. Bhatnagar S, Natchu MU. Coeliac disease in Indian children. Natl Med J India 2004 ; 17 :124-7.
6. Makharia GK. Where are adult Indian celiacs? Tropical Gastroenterol 2006;27:1-3.
7. Walker-Smith J, Guandalini S, Schmitz J, et al. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990; 65: 909-11.
8. Catassi C, Cellier C, Cerf-Bensussan N, et al. When is a coeliac a coeliac? Report of a working group of the United European Gastroenterology Week in Amsterdam, 2001 Eur J Gastroenterol Hepatol 2001;13: 1123-28.
9. Troncone R, Bhatnagar S, Butzner D, et al. European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Celiac disease and other immunologically mediated disorders of the gastrointestinal tract: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2004; 39 (Suppl 2):S601-10.
10. Hill ID, Dirks MH, Liptak GS, et al. Guidelines for the diagnosis of diagnosis and treatment of celiac disease in children: Recommendation of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005; 40: 1-19.
11. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003;163: 286-92.
12. Rewers M. Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease? Gastroenterology 2005 ;128 (4 Suppl 1):S47-51.
13. Fasano A. Where have all the American celiacs gone? Acta Paediatr 1996; 412 (Suppl): 20-24.
14. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology 2001;120: 636-51.
15. Cronin CC, Shanahan F. Exploring the iceberg- the spectrum of celiac disease. Am J Gastroenterol 2003;98: 518-20.
16. Lal S, Nain CK, Prasad KK, at al. Celiac disease in Chandigarh: A population survey. Indian J Gastroenterol 2005;24 (Suppl 1):A39.
17. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology. 1992; 102:330-54.
18. Marsh MN. The natural history of gluten sensitivity: refining and re-defining. Q J Med 1995; 85:9-13.
19. Collin P, Kaukinen K, Valimaki M, et al. Endocrinological disorders and celiac disease. Endocr Rev 2002; 23:464-83.
20. Sood A, Midha V, Sood N, et al. Increasing incidence of celiac disease in India. Am J Gastroenterol. 2001 ;96:2804-5.
21. Varma S, Malhotra P, Kochhar R, et al. Celiac disease presenting as iron-deficiency anemia in northern India. Indian J Gastroenterol. 2001; 20:234-6.
22. Sood A, Midha V, Sood N, et al. Incidence and prevalence of ulcerative colitis in Punjab, North India. Gut 2003; 52:1587-90.
23. Yang SK, Loftus EV Jr., Sandborn WJ. Epidemiology of inflammatory bowel disease in Asia. Inflamm Bowel Dis 2001; 7:260-70.
24. Makharia GK. Rising incidence and prevalence of Crohn's disease in Asia: is it apparent or real? J Gastroenterol Hepatol 2006;21:929-31.
25. Yao T, Matsui T, Hiwatashi N. Crohn's disease in Japan: diagnostic criteria and epidemiology. Dis Colon Rectum 2000;43 (Suppl): S85-S93.
26. Pulimood AB, Ramakrishna BS, Kurian C, et al. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. Gut 1999; 45:537-41.

27. Pulimood AB, Peter S, Ramakrishna B, et al. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. J Gastroenterol Hepatol 2005; 20:688-96.

28. Quyang Q, Tandon R, Goh KL, et al. The emergence of inflammatory bowel disease in Asian Pacific region. Curr Opin Gastroenterol 2005; 21:408-13.

29. Makharia GK, Banerjee D, Datta Gupta S, et al. Differentiation of Crohn's disease from intestinal tuberculosis in India. Indian J Gastroenterol 2004; 23 (Suppl): A40.

30. Chacon O, Bermudez LE, Barletta RG. Johne's disease, inflammatory bowel disease, and Mycobacterium paratuberculosis. Annu Rev Microbiol 2004; 58:329-63.

31. Morita N, Toki S, Hirohashi T, et al. Incidence and prevalence of inflammatory bowel disease in Japan; nationwide epidemiological survey during the year 1991. J Gastroenterol 1995; 30:1-4.

32. Phavichir N, Cameron DJ, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. J Gastroenterol Hepatol 2003; 18:329-32.

33. APDW2004 Chinese IBD Working Group. A retrospective analysis of 515 hospitalized Crohn's disease in China: A nationwide study from 1990 to 2003. J Gastroenterol and Hepatol 2006;21:1009-15.

34. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004; 126:1504-17.

35. Desai HG, Gupta PA. Increasing incidence of Crohn's disease in India: Is it related to improved sanitation? Indian J Gastroenterol 2005; 24: 23-4.

36. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347:417-29.

37. Weiss ST. Eat dirt- the hygiene hypothesis and allergic diseases. N Engl J Med 2002; 347:930-1.

38. Bach JF. The effect of infection on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002; 307:911-20.

39. Antia FP, Desai HG, Jeejeebhoy KN, et al. Incidence of intestinal helminthes in Bombay. Indian J Med Sci 1965; 18:635-8.