CROHN'S DISEASE: THE INDIAN PERSPECTIVE

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INTRODUCTION

Crohn's disease (CD) encompasses a multisystem group of disorders with specific clinical and pathological features characterized by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation primarily affecting the gastrointestinal (GI) tract. It is a multisystem disorder with potential for systemic and extra-intestinal complications (1) that can affect any age group, but the onset is most common in the second and third decades.

It is important to differentiate CD from other inflammatory diseases of the gut that can simulate or complicate its clinical course.[1] CD is a chronic inflammatory disorder that is neither medically nor surgically "curable" requiring therapeutic approaches to induce and maintain symptomatic control, improve quality of life, and minimize short- and long-term toxicity and complications.[2] Newer goals of therapy include the induction and maintenance of mucosal healing that are beginning to translate into changing the "natural history" of CD.[3,4]

The heterogeneity of manifestations, and the presence of overlapping features with other inflammatory bowel diseases, can make the diagnosis of CD difficult:[1]

- Characteristic symptoms of chronic or nocturnal diarrhea and abdominal pain, weight loss, fever, or rectal bleeding reflect the underlying inflammatory process.[5]
- Clinical signs include pallor, cachexia, an abdominal mass or tenderness, or perianal fissures, fistula, or abscess. Associated extra-intestinal features can include inflammation of the eyes, skin, or joints[6] and, in children anemia, fever, the failure of growth, or delayed development of secondary sex characteristics can be observed.[7]
- Although the onset is typically insidious, occasionally, CD can present in a fulminant manner at its onset or with the presence of toxic megacolon.[8]

Despite its potential heterogeneity, individual manifestations, and complications, there are definable patterns according to disease location and type (inflammatory, fibrostenotic, and fistulizing) that are important in determining clinical outcomes.[9]

INDIAN PRSPECTIVE

Inflammatory bowel disease (IBD) has traditionally been thought to be uncommon in India. Overall, the incidence and prevalence of CD in the Asia-Pacific region is reported to be lower than the estimated incidence and prevalence in North America or Europe.[10] Initial reports of CD in India included those of a few surgically treated patients who had presented with predominantly ileo-cecal stricturing disease.[11-13] Despite this, doubts persisted as to whether this was true CD in view of the widespread endemicity of intestinal tuberculosis in India, so much so, that a diagnosis of CD was met with derision.[14] However, in the past few years there has been a growing realization that, despite the high prevalence of intestinal tuberculosis, CD does occur in India.[15,16] This has been attributed to increasing awareness and availability of diagnostic facilities, coupled with improved sanitation, as is being seen in the rest of Asia. Despite this, only a few reports, involving a few patients, have been published

Table 1: Earlier surgical series on Crohn's disease from India

Author and year (Reference number)	Gupta, 1962 (11)	Tandon, 1972 (12)	Venugo-palan, 1980 (13)	Prakash, 1976 (30)
Region	East	North	South	North
Patient Number	44	10	21	13
Mean age in years	20-35	20-39	30	NA
Male/Female	1:1.4	4:1	3.2:1	2.3:1
Symptom		NA		
Pain abdomen	16%		NA	100%
Diarrhea	16%		4.8%	8%
Weight loss	14%		NA	38%
Fever	NA		NA	46%
Intestinal obstruction	20%		14.3%	15%
Lump abdomen	31%		24%	69%
Acute abdomen	14%		23%	NA
Location				
Ileum	31%	None	14.2%	None
Colon	14%	10%	19%	None
Ileocolonic	55%	70%	43%	100%
Perianal	None	40%	19%	None
Upper GI	2.3%	20%	4.8%	None
Complications		NA		NA
Fistula	4.5%		24%	
Stricture	32%		9.5%	
Abscess			4.8%	
Perforation			4.8%	
Cancer			4.8%	
Surgery	100%	100%	100%	100%
Follow up in years	1-5	NA	6-7	NA
Recurrence	11.4%	NA	33.3%	NA

NA: *no data available*

from India in recent years, and those have been retrospective, usually limited to a select group of patients with ileo-caecal or colonic CD,[16,17] or a subgroup of patients presenting with obscure gastrointestinal (GI) bleeding.[18]

Epidemiology of CD in India

Hardly there are any specific data that specifically looked in the frequency and determinants of disease distribution in this Country. Probert CS and colleagues made a candid attempt and carried out several retrospective community-based studies on Indian migrants in different countries. They found out that the minimum incidence on CD is $0.14/10^5$ persons year, overall Hindus have a much lower incidence of CD that Europeans, small bowel disease is inversely associated with age and colonic disease increases with age.[19,20] In addition, studies in rural Indian subcontinent (by Christian missionaries working in Mission hospitals or clinics) found that rate of cases having UC rather than CD greater in India and Bangladesh, than in Pakistan, Nepal or Bhutan.[21] A study by Montgomery SM *et al* has shown that young Asians who were born in Britain were at a significantly higher risk of developing IBD (both UC and CD) than the indigenous European population, even after adjustment for the potential confounding factors and family history of IBD.[22] In the South Asian CD cohort, disease location is predominantly colonic with less penetrating disease compared to Northern Europeans and a reduced need for surgery.[23]

The recent increase in the incidence of CD in populations from third world countries has been, in part, explained by overall improvements in sanitation and hygiene that diverted the everlasting heightened TH2 response to a pro-inflammatory TH1 response.[24]

Finally, Sood A *et al* have recently proposed the need to ensure uniformity in diagnosis and initiate a disease registry in order to accumulate accurate and authentic data on the epidemiology of CD in India.[25]

Genetics of CD in India

Three specific mutations in the NOD2 gene (whose product is a bacterial sensor on intestinal epithelial cells) lead to defective innate immune recognition of luminal microbes resulting in intestinal inflammation in CD and is found in up to 30% sporadic CD patients in the West. A study from CMC Vellore in 2005 found that none of the three mutations are associated with CD in this country.[26] In a well-characterized case-control cohort from South India incorporating 241 patients with CD, neither the NOD2 gene mutations (marker of innate immunity) nor the protective variant R381Q of IL23R gene (marker of adaptive immunity) were associated with CD.[27] Hence in Indian population, additional variants of these genes or other candidate genes might play a role in pathophysiology, as has been proposed.

There is preliminary data from a North Indian premier Institute that certain polymorphisms of TNF alpha genes is associated with enhanced IBD susceptibility (more so for UC than CD).[28] The same group has also found an association between allele 2 IL-1 receptor antagonist gene and CD, but not with UC.[29]

Clinical features of CD in India

Early Indian studies on CD,[11-13,30] were all surgical series where the disease presented with surgical problems and the diagnosis was established only post-operatively on histology hence the data are authentic (Table 1). One of them,[11] done from Eastern India, incorporated relatively large number of patients (total 44). All those studies have shown that CD was more common in males with onset in third or fourth decade. A large number of patients (24 to 69%) presented with lump abdomen and had intestinal obstruction (14 to 20%). Ileocolonic location was the commonest with perianal involvement in 19 to 40%. One of the studies[13] has categorically noted the complications and observed fistula in 24%, stricture in 9.5%, abscess in 4.8%, perforation in 4.8%, and cancer in 4.8%. None of the study made any observation regarding the presence of extra-intestinal manifestations. Over a follow up period of 1 to 7 years in different series, a disease recurrence rate of 11 to

Table 2: Recent series on Crohn's disease from India

Author and year (Reference number)	Pai, 2000 (16)	Ghoshal, 2007 (31)	Benjamin, 2008 (32)	Amarapurkar, 2008 (33)	Das, 2009 (34)
Region	South	North	North	West	Multicenter
Patient Number	25	16	125	26	182
Mean age in years	31.7	44	36	36.6	34.5
Male/Female	1.08:1	3.1	1.1:1	1.6:1	1.8:1
Duration before presentation	NA	NA	50 months	56 months	36 months
Symptom			NA		
Pain abdomen	84%	NA		65%	62%
Diarrhea	80%	44%		69%	68%
Weight loss	88%	NA		69%	57%
G I Bleed	44%	31%		31%	67%
Fever	16%	NA		23%	30%
Intest. obstruction	16%	31%		19%	28%
Lump abdomen	24%	6%		8%	6%
Acute abdomen	NA	6.3%		NA	NA
Location					
Ileum	None	NA	12.8%	61%	32%
Colon	76%	NA	49.6%	69%	41%
Ileocolonic	24%	NA	37.6%	NA	23%
Perianal	20%	6.3%	20%	8%	17%
Upper GI	None	NA	18.4%	12%	15%
Complications					
Fistula	NA	18%	11.2%	12%	8%
Stricture	16%	NA	29.6%	NA	28%
Abscess	4%	NA	NA	NA	2%
Perforation	NA	25%	NA	NA	NA
Cancer	None	None	None	None	None
Extra-intestinal manifestations	24%	NA	39.2%	61.5%	30%
Surgery	NA	19%	NA	35%	37%
Follow up in years	0.5 – 4.5	NA	NA	NA	NA
Recurrence	NA	NA	NA	78%	NA

NA: *no data available*

44% was noted.

The strong reservation regarding the existence of CD in India expressed in mid-1980s have now being strongly refuted by burgeoning number of recent reports from all corners of India.[16,31-34] The presentation with surgical problems are much less in recent times as increasing awareness and knowledge of natural history lead to early suspicion, diagnosis and treatment. Most patients, now diagnosed, have mild disease which is reasonably well controlled with medicines, but nearly one third need surgery in the long run.

The recent reports project similar age of onset (to that of earlier series) with a male predominance, long duration before presentation (36 to 56 months), and a higher complication rate (8-18% fistula, 18-29% stricture, 25% perforation, 30 to 61% extra-intestinal manifestation) (Table 2). Pain abdomen (62-85%), diarrhea (44 -80%), and weight loss (57-88%) are three predominant symptoms but still a significant number present with intestinal obstruction (16-31%). The important differences compared to earlier series are: increasing presentation with obscure GI bleed, colonic disease (though most of the studies do not mention isolated colonic disease) and extra-intestinal manifestations, but decreasing presentation with surgical problem with lesser number of operations but a high rate of recurrence.[33]

CD and malabsorption

In a study evaluating the etiological spectrum of sporadic malabsorption syndrome (MAS) in adults, CD was found in 10% (9 out of 99) and was as common as Celiac disease (and more common than tuberculosis) as a cause of MAS.[35] Patients with CD (compared to other etiologies of MAS) had relatively low albumin, low haemoglobin and required surgery more often. However, a recent study found that CD as a cause of MAS and chronic diarrhea is rare (~2%).[36]

CD and malnutrition

Patients with CD are often undernourished. Though there are several studies evaluating nutrition in CD patients (particularly children and adolescent) from the Western countries, data from India are scanty. One of the Indian studies included only 9 patients and found that several anthropometric parameters of nutrition were lower among IBD patients compared to healthy controls but without any significant difference between those with active disease and those in remission.[37] Another study included a large number of patients (total 112) and found 52.6% prevalence of malnutrition.[38] This study categorically showed that more patients in active disease (83%) was malnourished than in remission group (39%) but there was no difference in energy intake between the groups.

CD and bone metabolism

Two third of Indian patients with CD have low BMD particularly at the hip and spine region.[39] This is probably related to disease activity but has no relation with age, disease duration or cumulative steroid dose. Serum 25(OH) vitamin D levels are also significantly lower among patients with CD as compared to age and sex matched controls.[40] Further, levels are lower in those with severe disease activity and less sun exposure. Sunlight and vitamin D might protect against CD by downregulating the TH1 cells driven immune response.[41] While low serum vitamin D levels may tilt the immunological balance in CD, the disease process *per se* worsens the absorption of calcium and vitamin D from the gut and may set a vicious cycle.

CD and intestinal microbiota

The subsets of bacteria participating in the pathogenesis of UC and CD are likely to be different. Real time analysis using 16S rRNA-based genus-specific primers have shown

a clear delineation in concentration of bacteria between the predominating and subdominating genera.[42]

The role of Mycobacterium avium ss paratuberculosis (MAP) in the etiopathology of CD remains controversial, because of conflicting reports demonstrating the presence of MAP-specific insertion sequence from intestinal biopsy tissues of patients clinically diagnosed for the disease. In a study done at Hyderabad, MAP-specific IS900 DNA and RNA could not be detected by nested PCR in the intestinal tissues of any patient with CD.[43]

Pediatric CD in India

Malathi S *et al* from Chennai reported a series of 10 pediatric patients and that is the only available information from this country about pediatric CD.[44] These children were between 5-15 years of age and majority (8 out of 10) had primary colonic involvement. Complications such as stricture and fistula were identified in 4 of them. Frank rectal bleeding was seen in 25% and extra-intestinal features also in 25%. These children were managed medically except one who underwent surgery.

CD vs. abdominal tuberculosis

Abdominal tuberculosis resembles CD clinically and radiologically, and it may be difficult to differentiate between them, even at laparotomy or histology. The distinction is important, however, for proper management of the two conditions. Every effort must be made to exclude abdominal tuberculosis before the patient is diagnosed as having CD and is treated with steroids.[45] However, the problems of distinguishing these conditions have been repeatedly highlighted.[46] Simple clinical parameters like fever (in favor of tuberculosis), bleeding per rectum and diarrhea (both in favor of CD), and duration of symptoms (significantly longer in CD than tuberculosis) may give some clue but may not be useful in a given case.[33]

Segmental colonoscopic biopsies are often useful in the differentiation of ileocaecal tuberculosis from CD[47] The salient features of CD are small granulomas without caseation, focally enhanced colitis, pericryptal granulomatous inflammation, and the presence of architectural alteration/activity/chronic inflammation/deep ulceration at sites that did not show granulomatous response in the same or adjacent segments. There is an accrual in the number of diagnoses made with increasing numbers of biopsies from rectum to ileum.

Two studies from India involving large number of patients showed that anti-Saccharomyces cerevisiae antibody (ASCA) was not useful in differentiating between CD and tuberculosis.[31,17] Almost half of the patients with intestinal tuberculosis in both studies were ASCA-positive, which was comparable to the frequency in patients with CD. ASCA is a non-specific antibody resulting from macromolecular transport of food antigens (including antigens contained in baker's yeast), partly resulting from an increase in intestinal permeability. Since patients with intestinal tuberculosis have chronic inflammatory lesions of the small intestine, similar to patients with CD with increased small intestinal permeability, frequent positive results with the ASCA test in the former condition is quite expected.[31]

In a recent study, Makharia GK *et al* have evaluated clinical, endoscopic and histological criteria as predictor of differentiation using a multivariate analysis.[48] Blood in the stool, weight loss, focally-enhanced colitis, and involvement of the sigmoid colon were the most important features in differentiation between CD and intestinal tuberculosis. On the basis of regression coefficients of the final multivariate logistic model, a score that varied from 0.3 to 9.3 was devised. Higher score predicted more likelihood of intestinal tuberculosis.

Distinguishing features of these two entities are summarized (Table 3).[49] There is a recent brilliant review by Indian workers evaluating the available evidence regarding the usefulness and limitations of all these different modalities.[50]

Treatment of CD

There is even lesser information on the outcome of therapy of CD in India.

Fibro-stenotic disease and its associated complications are the predominant indications for surgery in CD. In a series by Das K *et al*, 37% patients required surgery.[34] Most of the surgical series have performed resection and anastomosis (with stricturoplasty in some cases and exteriorization in presence of frank peritonitis), and in the majority of the cases the disease did not recur. Postoperative morbidity is observed in 30% and anastomotic leak in 21%.[51] Preoperative anaemia, malabsorption and / or growth retardation, steroid and/ or immunosuppressant therapy and mid small bowel resection had a negative impact on anastomotic integrity. Indication of surgery, type or extent of disease and diverting stoma created at surgery did not have any impact on post-operative outcome.

In India, steroid is the commonest drug used for induction (in 37%) followed by 5-aminosalicylates (ASA) (17%).[34] Interestingly, 14% receive ATT in the initial phase and 38% patients who were initially treated with ATT had some symptomatic response but majority relapse in the follow up. Large majority of patients in India receive 5-ASA as maintenance therapy either alone (63%) or in combination with azathioprine (AZA) (21%) with majority of them maintaining remission. This could be due to higher percentage of cases with disease at colonic location and / or inflammatory behavior. The use of AZA has not gained wide acceptance in India as a safe maintenance therapy till date.

There are isolated reports of use of biologicals from India.[52] However, their role both in induction and maintenance have

Table 3: Differentiation of Crohn's disease (CD) from intestinal tuberculosis[IT]

Parameter	CD	IT
Age (years)	20-50	Any age
Gender (male:female)	3:1	1:3
Partial intestinal obstruction	Occasional	Frequent
Anorectal disease	~ 25%	~ 8%
Fistulae	Common	Rare
Colonoscopy/endoscopy		
Ulcers	Longitudinal orientation	Circumferential orientation
	Adjacent mucosa normal	Adjacent mucosa inflamed
	Aphthous ulcers common	Aphthous ulcers uncommon
Cobblestoning	Frequent	Hyperemic nodules
Ileo-cecal valve	Preserved architecture	Destroyed in 80%
Segmental colitis	~ 80%	~ 40%
Barium radiology		
Strictures	Long	Short
	Often multiple	Usually single
Skip lesions	Frequent	Rare
CT/MRI abdomen		
Wall thickening	Symmetric	Asymmetric
Mesentery	'Creeping fat' or '**comb** sign'	Nodularity, abcesses, 'caked' omentum
Lymph node enlargement	Usually regional, 3-8 mm	Regional and/or retroperitoneal, 12-550 mm
	Homogeneous enhancement	Enhancing rim with central low attenuation
Ascites	Rare	Common
Endoscopic biopsy / histopathology		
Granulomas	30-60%	80-100%
Caseation	0	~40%
Confluent granulomas	0	40-60%
>5 granulomas/site	0	40-45%
Large granulomas (>400 μm)	0	50%
Submucosal granulomas	5-6%	40-45%
Disproportionate submucosal in inflammation	5-10%	~65%
Acid-fast bacilli (AFB) on smear	0	~30%
TB DNA analysis positive	0-5%	22-75%

not been conducted in properly designed trials. The use of biological, at the most, remains experimental and Institution-specific.

CONCLUSION

India is a vast country with a multi-linguistic population of differing race, genetic set up, culture and dietary habits. IBD particularly CD is an emerging problem in this country and the clinical data on this disease and its temporal trend is rarely available. This review is a sincere attempt to understand the dimension of CD in India by accumulating the scarce clinical data so as to enlighten the practicing physicians and the students of medicine about the disease characteristics.

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