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Profile And Time Trends of Crohn's Disease in North Kerala - A Twelve Year Audit

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Abstract
Crohns disease is a chronic inflammatory bowel disorder characterized by transmural granulomatous inflammation affecting any part of the GI tract. Although CD is rarer than intestinal TB in India, there is compelling data that indicates its rising incidence. There is a lack of systematic data regarding the characteristics and time trends of Crohns disease from South India. We performed a retrospective analysis of patients over a 12 year period attending the IBD clinic of our teaching hospital that caters to 6 districts of north Kerala. Our study showed a clear rising trend of Crohns disease in North Kerala. Weight loss, abdominal pain and diarrhea were the most common modes of presentation. 40% of our study cohort had received ATT which led to considerable delays in diagnosis of CD. Diagnosis was delayed compared to the West but nearly a year earlier compared to North India.

Keywords: Crohns disease; Intestinal tuberculosis; inflammatory bowel disease; South Indian study

INTRODUCTION

Crohn's disease (CD) is a form of inflammatory bowel disease which can involve any part of GIT.It arises due to a complex interplay between genetic and environmental factors and is said to be more common in developed countries. A rising trend in the incidence and prevalence of CD has been observed in Asian countries like China, Korea and Japan.[1-2].Rising frequency in Asian countries could be attributed to rapid industrialization and urbanization as reported in Europe in mid 1990s. [3]

Tuberculosis(TB) is endemic in India. Resurgence of TB has been noted in western countries due to pandemic of human immunodeficiency virus infection and trans-global migration. Initially there was a lot of skepticism when CD cases were reported from India mostly in the setting of ileocecal structuring disease..[4]However, currently there is compelling evidence that CD is prevalent in India.[5-8]This may be due to increased physician awareness, availability of diagnostic techniques as well as a true rise in incidence.

There is a lack of systematic data regarding the characteristics and time trends of CD from South India. Therefore we performed a retrospective analysis of cases diagnosed with CD including both hospitalized as well as outpatient subjects.We aimed to describe the clinical features, disease behavior and time trends of CD among patients from six districts in northern Kerala who attend our teaching hospital.

METHODS

Patients

Case records of patients with a diagnosis of CD from January 2001 to December 2012 were reviewed after

getting due approval from institutional ethics committee. If a patient with CD had been in hospital several times, only the first medical record was reviewed. The date of the first admission was used to analyze the time trends over 12 years. All the data were systematically entered in a standard proforma. Information regarding patient demographics, duration of disease, clinical manifestations, endoscopic, radiologic and histologic features, surgical interventions, drug therapy(steroids,immunomodulators,mesalamines,biologics,antibiotics) and outcome of disease were finally entered into Microsoft excel chart.

Diagnostic criteria

Diagnosis of CD was based on a combination of clinical, radiologic, endoscopic and histologic features along with lack of response to/relapse after a trial of antitubercular therapy. Other compatible aetiologies like tuberculosis, amoebiasis and lymphoma were excluded. Diagnostic criteria were applied after the data had been entered into excel chart. Definite CD was diagnosed if patients satisfied any of the following criteria (1) those who met the World Health Organization(WHO) criteria (table 1) for definite CD[1] (2) those who did not meet the WHO criteria of definite CD but whose histology was compatible with CD [according to the European Crohn's and Colitis Organization (ECCO)] [9] guidelines] or whose condition had shown no response to or had relapsed after at least 4–8 weeks of anti-tubercular therapy (ATT) as per the management consensus for IBD for the Asia-Pacific region[10](3) those who met the WHO criteria for probable CD and had diagnostic macroscopic (e.g., fat wrapping) or radiologic/ colonoscopy (rectal sparing, ileal disease) features compatible with CD (ECCO guidelines).Only those with a diagnosis of definite CD were included in the analysis. Disease behavior was classified according to the Montreal classification, taking into account the age at onset, location and disease behaviour[11].

Statistical methods

Mean, median, standard deviation (SD), range, and proportions were calculated as appropriate. Categorical variables were analyzed using the chi-square test and continuous data were analyzed using the Mann–Whitney U test.

RESULTS

Patients: A total of 113 patients were diagnosed with CD between 2001 and 2012.There were 57 males and 56 females. The CD ratio of male to female was 1.01 showing no sex predominance of CD cases. Age at presentation ranged from 13 to 72 years .Mean age at diagnosis was 32.38 years. Duration of symptoms prior to diagnosis ranged from 1 month to seventeen years. Median duration of symptoms was 24.5 months.Figure1 depicts age specific cases of CD.Highest prevalence of cases was noted in the 20-40 year age group. Table 2 shows the year specific ratio of CD cases to all hospitalized patients between 2001 to 2012. The ratio in 2012 (22.2×10^{-5}) is 3.31 times higher than that in 2001(6.7×10^{-5}).

Clinical manifestations: The most common mode of presentation was with weight loss in 85 cases (75.2%) and abdominal pain in 82 cases (73.3%) followed by chronic diarrhoea in 71 cases (62.8%) and fever in 20 cases (19%).Among the patients who presented with diarrhoea,large majority(> 83%) had large bowel type/bloody diarrhea. Anemia or occult GI bleed (36%),overt GI bleed (30%) and intestinal obstruction(26%) were the most common intestinal complications. Perianal disease was noted in 21 (18.5%) cases. Perianal fistula (7%) was the most common perianal manifestation followed by fissure (4.4%),perianal abscess (3.4%) and perianal ulcer (2.6%).Only one patient had malignancy in the form of small bowel adenocarcinoma which presented as intestinal obstruction within 6 years of the onset of symptoms. Extra intestinal manifestations were noted in 22 (19.4%) cases. Aphthous ulcer(8.8%) and arthralgia(8.8%) were most common followed by arthritis (4.4%) and erythema nodosum (4.4%).True sacroilieitis (1.9%) ,spondylitis (0.95%) , and primary sclerosing cholangitis (0.95%) were rare. Table 3 shows the various clinical manifestations.

Diagnostic investigations: Colonoscopy with mucosal biopsy, barium meal follow through for assessment of small bowel and cross sectional imaging with contrast enhanced CT abdomen were the principal diagnostic modalities. All patients underwent colonoscopy.46 (40.7%) patients underwent colonoscopy twice. Cecum (46%)ileocecal valve (42.4%) and ileum (38.9%) were the most common colonic segments involved. Nodularity (51.3),aphthous ulcers(42.4) and linear ulcers

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(38.9%) were the most common lesions found.76 (67.2%) patients underwent barium meal follow through. Narrowing of bowel lumen, thickened bowel and dilated loops were the most common findings. Other features like string sign, cobblestoning and aphthous ulcers were seen less often.52 patients underwent CT abdomen. Bowel wall thickening (29.2%), mesenteric fat stranding (21.2%) and narrowing of bowel lumen (14.1%) were the most common findings (Table 4).

Histology was available in 107 patients of whom 101 were colonoscopy biopsies and 12 were surgical specimens. In endoscopic biopsies, chronic colitis (107 cases,100%) and mucosal ulcerations(81 cases,75.7%) were the most common findings. Mirogranulomas were observed in 48 cases (44.8%).Of the 12 surgical specimens, granuloma was present in 8 cases (66.8%).(Table 5)

Antitubercular therapy(ATT) :Information regarding ATT was available in 110 patients.44 (40%) patients had history of ATT.All patients have received only one course of ATT. Duration of ATT varied from 1 to 18 months, mean duration being 5.5 months. The risk factors for receiving ATT were shorter duration of symptoms, ileoceacal involvement, and inconclusive colonic biopsy reporting by pathologist. Data regarding clinical response to ATT was available in all cases.19 out of 44 patients (43.1%) had improvement in clinical symptoms while on ATT.25 out of 44 patients (56.8%) had worsened after starting ATT.In the large majority of cases, the possibility of CD was considered initially. However empirical ATT was given due to lack of typical radiological/endoscopic/pathological features of CD.The diagnosis was revised to CD based on lack of clinical improvement/ endoscopic mucosal healing in response to ATT.

Phenotypic classification of the disease: The phenotype of disease was assessed using the Montreal classification which is as follows.Age at onset A1:A2:A3 11%:65%:24%.Location of disease L1:L2:L3 20%:51%:29%.Disease behavior B1:B2:B3 65%:28%:7%. 6 (5%) and 21 (19%) patients had upper GI and perianal modifiers respectively.

Surgical intervention:28 out 113 cases (24.7%) underwent some form of surgical intervention.Segmental bowel resection and anastomosis (9 cases,8%) was the most frequently performed procedure followed by right hemicolectomy(5 cases,4.4%).4 cases (3.5%) underwent appendectomy.(Table 6)

Treatment: Data regarding drug therapy was available in 105 cases. The medications used were 5 amino salicylates in 77(73%), steroids in 65(62%) , azathioprine in 52(50%) and antibiotics in 46(44%).Methotrexate was not used in any patient.3 patients received induction of remission with infliximab.

DISCUSSION

This is the first large scale systematic study of Crohn's disease from Kerala. This is a retrospective study of hospitalized Crohn's disease patients during the period 2001 to 2012.Ours is a tertiary reference centre in North Kerala providing medical care to the six districts of Calicut, Malappuram, Wayanadu, Kannur, Kasargodu and Palakkad.

A total of 113 cases of definite CD were diagnosed during the period.There is a clear rising trend in the incidence of new cases from 2001 to 2012.The year specific ratio of CD cases to all hospitalized patients more than tripled towards the end of the study period. Ratio in 2012 is 22.2 x 10^{-5} compared to that in 2001($6.7x10^{-5}$)This rising trend has been noted in many other countries where CD was rare compared to the West.[12-15]. In Kerala, more awareness about the disease, better diagnostic facilities and growth of gastroenterology as a separate specialty also might have contributed to detection of more cases,apart from a true rise in the incidence of the disease. Improvement in sanitation and public health leads to a decline in infectious disease burden while associated with a rise in autoimmune and chronic inflammatory diseases[16]The study The study by Pughazhendhi et al [17]from Vellore looked into surrogate markers of environmental hygiene in CD cases compared to age matched healthy controls.The study found that urban residence,safe drinking water and availability of piped water(all markers of better hygiene) were positively associated with CD cases.In view of the invasive and expensive nature of investigations needed to diagnose CD,it is possible that the diagnosed cases represent only a fraction of the total burden of disease. Milder forms of the

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disease may be missed leading to underestimation of its true incidence.

The mean age at diagnosis was 32 years in our study. Peak incidence was noted in the 3rd and 4th decades of life. A similar trend was noted in the multicenter Chinese(1) and Indian(5) studies conducted in the past.But in the West, Crohn's disease is diagnosed most often in the 15-30 year age group.[18].There were no cases of pediatric Crohn's disease in our series,the youngest patient being 13 years old.This could possibly due to referral bias as our centre caters to only adult patients. There was a slight female predominance in our study which matches the data from West[18-20]but was against the trend seen in a previous multicenter Indian study[5]

Median delay till diagnosis in our study was 24.5 months. In the past a mean delay of more than 3 years was reported from the west [21] but with heightened awareness of the disease and better diagnostic techniques, mean delay of less than one year has been described from west[22].Data from North and Eastern India showed a mean delay of 3 years before proper diagnosis was made. Hence it may be concluded that delay in diagnosis in Kerala is somewhere between that in North India and the West. There was a considerable delay in older patients(4.2 years in > than 40 year age group v/s 1.7 years in < 40 year age group P value <0.05).Patients who were initially treated with ATT had a longer delay in diagnosis compared to the rest.(3.2 years v/s 1.8 years P<0.05).Hence while irritable bowel syndrome [23] is one of the reasons for delayed diagnosis of CD in the West, older age and intestinal tuberculosis were the major reasons for late diagnosis in our cohort.

Clinical features at presentation included abdominal pain, diarrhea and weight loss which is in tandem with data from West[24],China[1] and North India[5].Stricturising disease was seen in 28%.Similar figures were noted from West[25],China[1] and North India[5].But penetrating disease was seen in 7% only which is much less than that in West and North India. The frequency of extraintestinal manifestations like arthralgia, aphthous ulcers etc were much less compared to data from West and North India.

Nearly 40% of patients had received ATT.Nearly 40% of Indian population is infected with tubercle bacillus and intestinal tuberculosis is quite common. Clinical, radiologic, endoscopic and often histopathologic differentiation between the two entities is challenging. Treatment with ATT had led to considerable delays in the diagnosis of CD. However there was no difference in the incidence of penetrating and stricturising disease between those who received ATT and those who did not.43% of patients who received ATT had initial improvement in clinical symptoms which led to full course of ATT. This 'therapeutic effect of ATT' in CD has been found in previous studies as well[5,26] but the evidence is rather weak. None of the patients who were given ATT had any microbiological evidence of tuberculosis. But this is not surprising, given the fact that intestinal tuberculosis is a paucibacillary disease and demonstration of the organism by histology or culture has a low yield.In patients who present with symptoms and signs suggestive of CD,empirical ATT is a valuable option especially when typical radiologic/ endoscopic/histopathologic features of CD are lacking. These patients have to be carefully followed up to avoid delays in diagnosis of CD. Combining histopathology with TB PCR of mucosal biopsies is a helpful technique to differentiate between CD and intestinal tuberculosis[29].However TB PCR was not routinely done in our study.

Microgranulomas were observed in 26% cases of endoscopic biopsies and 67% cases of surgical specimens. This figure matches data from West[28] and North India[5].None of the patients with microgranulomas had received ATT.

Treatment strategies were similar to that used in the west. Induction of remission was with steroids and 5 aminosalicylates in most cases. Maintenance therapy was done using azathioprine and 5 aminosalicylates. Only 3 patients received Infliximab for induction of remission.

The main findings of the study are as follows 1.There is a clear rising trend in the incidence of Crohn's disease in North Kerala 2.Colon was the most common site of involvement 3.Most CD patients are young and no sex predominance was seen 4.Diagnosis is delayed compared to west but nearly a year earlier than that in Northern India 5.Weight loss, abdominal pain and diarrhea were the most common modes of presentation 6. Presentation as appendicitis was unusual 7.Anemia,overt lower GI bleed and

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intestinal obstruction were the most frequent complications 8.Extraintestinal manifestations were less common 9.Penetrating disease was less common 10.Microgranulomas were seen in 26% of endoscopic biopsies and 67% surgical specimens 11. 40% had received ATT which led to considerable delays in diagnosis of CD.

Ours is a retrospective study during the period 2001-2012.The merits of the study are relatively large patient numbers, inclusion of only definite cases of Crohn's disease, use of colonoscopy and mucosal biopsies in 100% of cases while CT abdomen and small bowel radiologic evaluation was done in the large majority. Our limitations include exclusion of pediatriac cases if any and referral bias as the study was done on a tertiary centre based patient population.

TABLES & FIGURES

Table 1: World Health Organization diagnostic criteria for Crohn's disease*

Item	Clinical	Radiological	Endoscopy	Biopsy	Resected specimen
1. Discontinuous or segmental lesions		+	+		+
2. Cobblestone appearance or longitudinal ulcer		+	+		+
3. Transmural inflammation	+ (Abdominal)	+ (Stricture)	+ (Stricture)		+
4. Non-caseating granulomas				+	+
5. Fissures and fistula	+	+			+
6. Perianal disorders	+			+	+

*A definite diagnosis was made when either 1+2+3 were present with any one of 4/5/6 or when 4 was present with any two of 1/2/3

Table 2: Year wise distribution of CD cases and ratio to total hospital admissions per year

Year	Total hospital admissions	CD cases diagnosed	Ratio of CD cases to all hospitalized patients(x 10^{-5})
2001	74245	5	6.7
2002	71333	4	5.6
2003	72742	7	9.6
2004	72247	9	12.5
2005	73291	6	8.2
2006	73094	8	10.9

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2007	73390	11	15
2008	77800	10	12.9
2009	76299	9	11.8
2010	71198	15	21.1
2011	76023	13	17.1
2012	72234	16	22.2

Figure 1: Age distribution of Crohn's disease(X axis -Age group in years: Y axis- Number of patients)

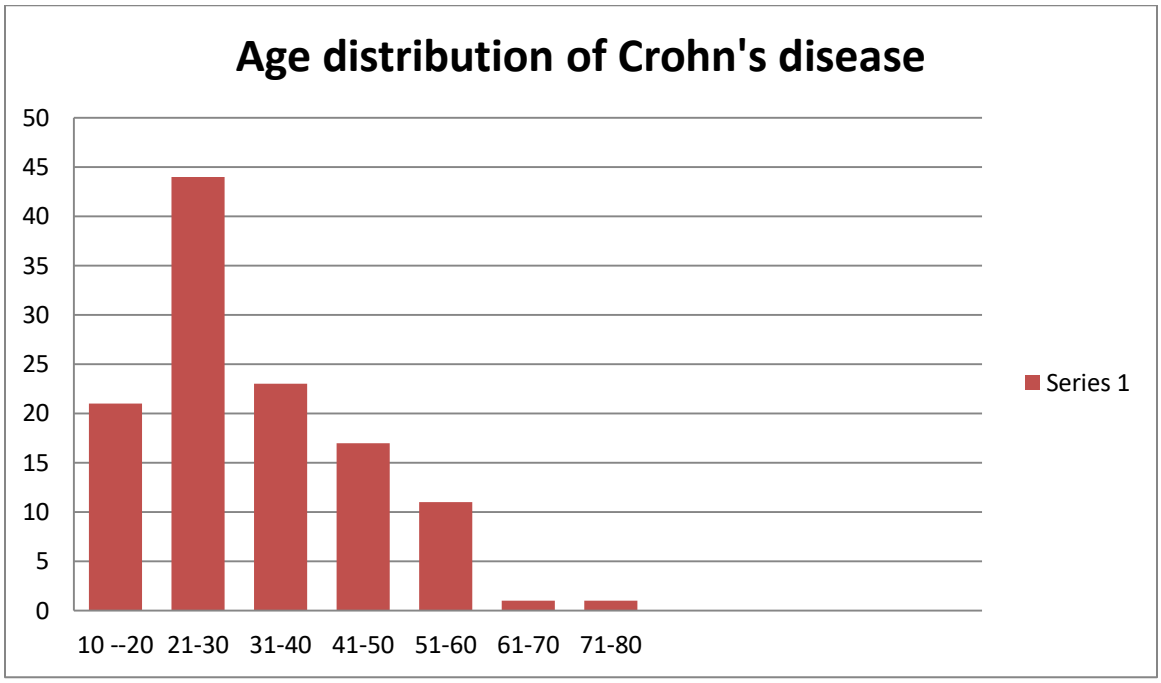

Table 3 Clinical manifestation of 113 CD cases

Clinical manifestations	Patients(n)	%
Symptoms and signs		
Weight loss	85	75.2
Abdominal pain	82	73.3
Diarrhoea	71	62.8
Fever	21	19%
Abdominal mass	5	4.4%

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Intestinal complications		
Anemia	41	36.1
Overt GI bleed	34	30.4
Intestinal obstruction	30	26.6
Perforation	2	1.7
Intra abdominal abscess	1	0.88
Malignancy	1	0.88
Gastric outlet obstruction	3	2.6
Perianal disease	21	18.5

Extraintestinal manifestations		
Arthralgia	10	8.85
Oral aphthous ulcer	10	8.85
Fatty liver	8	7.08
Arthritis	5	4.42
Erythema nodosum	5	4.42
Sacroileitis	2	1.9
Spondylitis	1	0.95
Primary sclerosing cholangitis	1	0.95
Episcleritis	1	0.95

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Table 4:Findings of colonoscopy in 113 CD cases

Items	N	Percentage
Colonoscopy(n=113)		
Involvement of individual colonic segments		
Perianal	10	8.85
Rectum	30	26.5
Sigmoid	32	28.3
Descending colon	28	24.7
Transverse	32	28.3
Ascending	36	31.8
Cecum	52	46
IC valve	48	42.4
Ileum	44	38.9
Colonoscopic findings		
Erythema	22	19.4
Friability	8	7
Linear ulcer	44	38.9
Aphthous ulcer	48	42.4
Transverse ulcer	16	14.1
Nodularity	58	51.3
Pseudopolyp	3	2.6
Cobblestoning	6	5.3
Stricture	14	12.3
Edema	16	14.1
Deformed segment	14	12.3
Skip lesion		
Serpiginous ulcer	5	4.4
Growth		

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fistula	6	5.3

Table 5: Histopathologic features of CD cases

Histologic findings		
Colonoscopic biopsies(n=107)		
Finding	N	%
Ulcer	81	75.7
Chronic colitis	107	100
Granuloma	28	26
surgical specimens(n=12)		
Transmural inflammation	12	100
Granuloma	8	66.66
Ulcer	5	41.6

Table 6: Surgical intervention

Type	no	%
Fistulectomy	4	3.5
Appendicectomy	4	3.5
Perforation closure	2	1.7
Right hemicolectomy	5	4.4
Stricturoplasty	2	1.7
Resection anastomosis	9	7.9
Gastrojejunostomy	2	1.7

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