original article

Childhood onset of Crohn disease: experience from a university teaching hospital in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Crohn disease (CD) is an increasingly recognized problem in Saudi Arabia. The aim of this study was to describe the clinical pattern in children and adolescents with CD seen at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

DESIGN AND SETTING: Retrospective hospital-based study conducted on data collected for the period between January 2001 and March 2010.

PATIENTS AND METHODS: Data for all children and adolescents diagnosed at KAUH with CD in the period were retrieved and analyzed.

RESULTS: Ninety-six patients were identified. The median age at diagnosis was 11.3 years (range, 0.12-17.6 years). Fifty (52.1%) were males. Sixty-four (66.7%) were Saudis. Nine (9.4%) had a first degree relative with inflammatory bowel disease. The most common presenting symptoms were diarrhea (88.5%), weight loss (84.2%) and anorexia (80.2%). At least one extraintestinal manifestation occurred in 24% of patients. Forty-two percent were underweight and 19% had short stature. The most common distribution was ileocolonic (37.5%), followed by colonic in 31.2%. Twenty-five (26%) patients had perianal disease, 13 (13.5%) had strictures and 15 (15.6%) had penetrating disease. Laboratory investigations revealed anemia in 84.4%, thrombocytosis in 50%, hypoalbuminemia in 64.6%, elevated erythrocyte sedimentation rate (ESR) in 50% and elevated C-reactive protein in 58.3%. Induction of remission was achieved with enteral nutrition in 20% of patients and with corticosteroids in the remaining.

CONCLUSIONS: The clinical pattern of CD in children from the Western Province of Saudi Arabia was found to be similar to reports from the West. Pediatricians should be aware of the varying presentations of CD. Early referral to specialized centers is crucial.

Inflammatory bowel disease (IBD) comprises Crohn disease (CD) and ulcerative colitis (UC), both lifelong chronic inflammatory conditions of the gastrointestinal tract arising in previously healthy individuals. Up to 25% of patients with IBD first present in childhood. The underlying etiology and pathogenesis of IBD remain largely unknown, but it is thought to result from an interaction between genetic susceptibility, environmental factors and the host immune response. CD is traditionally described as a patchy inflammation affecting any part of the gastrointestinal tract from mouth to anus, with discontinuity in affected areas. CD can affect all layers of the gastrointestinal tract and can proceed to strictures or fistula.[1,2]

IBD has been regarded as a disease primarily occurring in Western populations.[3,4] It was thought that IBD was rare or nonexistent in Saudi Arabia.[5] The first reported case of CD in Saudi Arabia was in 1982.[6] Since then there have been many reports of CD of adults in Saudi Arabia from different regions, including both urban and rural areas.[7,8] There has been a marked global increase in the incidence of IBD, particularly in pediatric populations.[9] There are reports of an increase in CD among children in Saudi Arabia. Toonisi[10] and El

Mouzan et al[11] reported the occurrence of CD in 17 and 19 children respectively. The aim of our study was to describe the clinical pattern in children and adolescents with CD attending the pediatric gastroenterology clinic at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia in the period between January 2001 and March 2010.

PATIENTS AND METHODS

We conducted a retrospective study of all children and adolescents with CD seen at KAUH between January 2001 and March 2010. A list of patients was generated by accessing the ICD-10 codes of the hospital admissions database. This data was augmented with data from an endoscopy unit database to ensure that all possible patients during the study period were included. Patients with CD were selected from the list of patients with IBD, where chronic inflammation of all or part of the digestive tract was documented. The diagnosis of CD was made in accordance with ESPGHAN Porto Criteria.[12] Relevant clinical and demographic information from all identified patients was recorded. Colonic infections were excluded by repeated stool examination and culture.

TB was excluded on the basis of a detailed family history, imaging studies, a negative purified protein derivative (PPD) test result and a negative PCR- hybridization of *Mycobacterium tuberculosis* on biopsy tissue obtained during colonoscopy. Follow up information for disease progression and outcome were retrieved from patients' charts. The anatomical extent of CD was determined by the initial colonoscopy, upper endoscopy and radiological studies. The distribution of CD was defined according to the Vienna classification where L1 stands for ileal, L2 for colonic, L3 for ileo-colonic, and L4 for disease in the upper gastrointestinal tract. The behavior of the disease was classified into B1 for non-stricturing non-penetrating, B2 for stricturing and B3 for penetrating disease.[13] Clinical remission of the disease was defined as the disappearance of clinical symptoms with normalization of the inflammatory markers including CRP and ESR.

The z scores for weight and height were calculated by using an anthropometric software program (Epi-Info, Centres for Disease Control and Prevention, Atlanta, GA, USA). Statistical analyses were performed using SPSS 19 software (IBM Corp, Armonk, New York, United States). Data were expressed as percentage of the total for categorical variables, as mean with standard deviation (SD) for normally distributed continuous variables, or as median with interquartile range for skewed distributed variables. A comparison of study groups was performed using the chi-square test for variables. All statistical analyses utilized a .05 level of significance. This study was approved by the Research Ethics Board at KAUH.

RESULTS

From January 2001 to March 2010, 157 children and adolescents with the diagnosis of IBD were identified at KAUH. Ninty-six patients were diagnosed with CD, which constituted 61.5% of the total IBD cases. The diagnostic modalities performed for these patients are shown in **Table 1**. The number of new CD cases diagnosed each year is presented in **Figure 1**. The median age at diagnosis was 11.3 years (range, 0.12-17.6 years). The age distribution is shown in **Figure 2**. Fifty (52.1 %) were males. Sixty-four (66.7%) were Saudis, while 24 (25%) were non-Saudis and 8 (8.3%) were nonArabs. First-cousin type consanguinity was present in 20 (35%) of the cases. A family history of IBD was present in 9 (9.4%) patients. Eight had affected siblings (7 had CD and 1 had UC) and 1 had an affected parent with UC. The concordance rate for CD was 78%.

The presenting symptoms are shown in **Table 2**. The median duration of symptoms prior to presentation was 8 months (range, 1-48 months). The most common extra-intestinal manifestation (EIM) observed was oral manifestations that occurred in 18 (18.6%) patients. Oral manifestations included angular cheili-

Table 1. Diagnostic modalities in the 96 patients.

	Number	Abnormal findings, n (%)
Endoscopy		
Colonoscopy with ileal intubation	90	88 (98)
Colonoscopy without ileal intubation	6	6 (100)
Upper endoscopy	27	4 (15)
Imaging		
Barium meal and follow through	66	49 (74)
Small bowel enema (enteroclysis)	13	11 (85)
CT scan with contrast	16	13 (81)
MRI	7	4 (57)
Histopathology		
None caseating granuloma	21	(22)

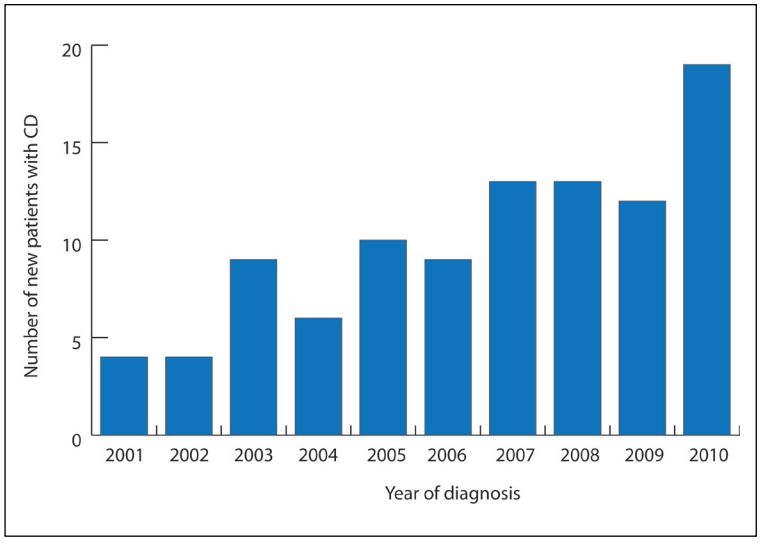

Figure 1. The number of new cases of Crohn disease diagnosed each year.

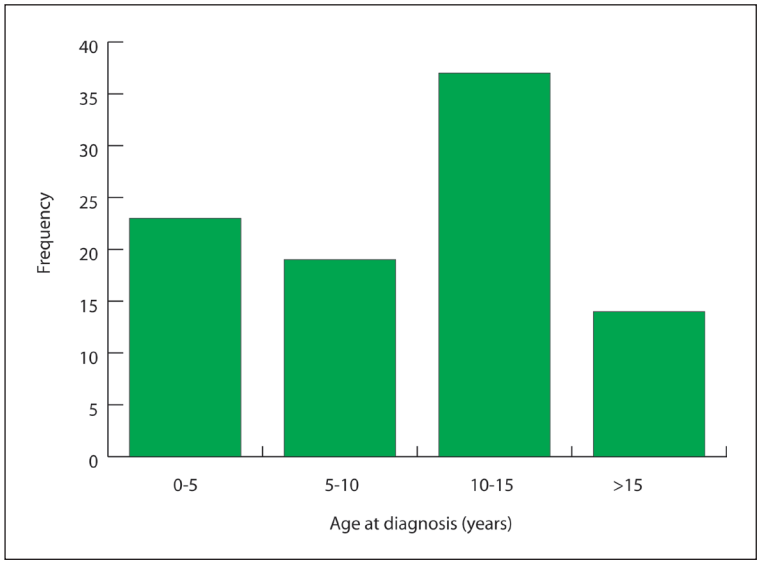

Figure 2. The age distribution at the time of CD diagnosis (n=96).

tis (n=9), apthous ulcerations (n=7), deep ulcerations of the tongue (n=3), mucogingivitis (n=2) and linear ulcerations of the buccal mucosa (n=2). There was no association between the type of oral involvement and either the disease phenotype or the presence of perianal disease (chi-square, *P*=.16 and *P*=.14 respectively). Two patients suffered from eye involvements, one had uveitis and the other had keratitis. Two (2%) had concomitant type-1 autoimmune hepatitis. Both had elevated transaminases at diagnosis. The diagnosis was confirmed by positive serology for anti-smooth muscle antibody compatible liver histopathology and normal magnetic resonance cholangiopancreatography. Both responded to treatment with corticosteroids. One patient had peripheral arthritis and one had skin vasculitis.

Lung involvement was observed in a 15 year-old girl who presented with chronic cough, diarrhea and weight loss. Her chest x-ray showed bilateral patchy alveolar opacities affecting mainly the upper lobe with increased mediastinal shadow. Chest CT scan showed a prominent right hilar lymph node and patchy areas of consolidation more seen in the right lung apex with bilateral scattered ill-defined confluent air space-opacities scattered in both lung fields. Workup for TB and immunodeficiency was negative. In spite of treatment with appropriate antibiotics she continued to have persistent symptoms and radiological abnormalities. Her lung condition resolved completely following the diagnosis and treatment with corticosteroid followed by maintenance with azathioprine.

At diagnosis, the median weight for age z-score was -2.26 (range, -11.6 to 2.3), while the median height for age z-score was -1.52 (range, -9 to 1.28). Forty-two percent had weight for age z-score less than -2.5 and 19% had height for age z-score less than -2.5. The median body mass index (BMI) z-score was -1.1 (range -10.4 to 9.6). 35% of patients had BMI z-scores less than -2.5. The difference between the means of weight and height z-scores between patients with different disease locations was not statistically significant (ANOVA, *P*=.78 and *P*=.52 respectively) which indicates that growth is equally affected regardless of the disease distribution.

The disease phenotype according to Vienna classification is shown in **Table 3**. The most common distribution was ileocolonic. Gastric involvement occurred in four patients, but isolated gastric involvement was seen in only one patient. An isolated colonic distribution occurred more frequently in younger children, while ileal and ileocolonic involvement occurred more frequently in older children. The mean age (SD) for the group with isolated colonic involvement (n=33) vs. the mean age (SD) for the group with ileal involvement (n=62) was 6.7 (5.3) vs. 11.3 (4.2), *P*<.001.

Twenty-five (26%) patients reported in this series had perianal disease other than perianal fistulae. Perianal disease varied from isolated skin tags to severe perianal ulceration. Chronic multiple anal fissures were diagnosed in 15 patients. Skin tags were present in 12 patients. Three had isolated skin tags, while 4 had severe ulcerations in the natal cleft and 3 had perianal abscesses. Perianal disease was the only presenting sign in

Table 2. Presenting symptoms in the 96 patients with Crohn disease.

Symptoms	Number	Percentage
Diarrhea	85	88.5
Weight loss	81	84.4
Anorexia	77	80.2
Abdominal pain	74	77
Passage of mucus	37	38.5
Bleeding per rectum	35	36.5
Fever	28	29.2
Vomiting	20	20.8
Tenesmus	10	10.4

Table 3. The disease phenotype according to Vienna classification (n=96).

	Number	Percentage
Location		
Ileal (L1)	29	30.2
Colonic (L2)	30	31.3
Ileo-colonic (L3)	36	37.5
Upper gastrointestinal (L4)	1	1
Behavior		
Non-stricturing non-penetrating (B1)	68	70.83
Stricturing (B2)	13	13.54
Penetrating (B3)	15	15.63

two (2%) patients.

Strictures were identified in 13 (13.5%) patients. These strictures were inflammatory, affecting only the small bowel. Eleven patients had involvement of both proximal and distal ileal loops. Three had jejunal strictures and two had distal duodenal strictures. The stricturing complications were associated with small bowel disease (chi square, P=.04). Penetrating complications occurred in 15 (15.6%) patients, presenting with perianal fistulae in 11 and internal fistulae in 4 patients. The internal fistulae were ileo-ileal (n=2), ileo-sigmoid (n=1) and ileo-vesical (n=1). Penetrating complications were not correlated with disease location (chi square, P=.7).

Eighty-one (84.4%) patients were anemic at diagnosis with a mean (SD) hemoglobin level of 10.2 (1.6) g/dL (normal, 12-14.5 g/dL). Thrombocytosis was present in 48 (50%) patients with a mean (SD) platelet count of 664 (193)$\times 10^3/\mu L$ (normal, 150-450$\times 10^3/\mu L$). Sixty-two (64.6%) patients had low albumin with a mean (SD) albumin level of 25 (7.2) g/L (normal, 35-50 g/L). The erythrocyte sedimentation rate (ESR) was high in 48 (50%) of 70 patients tested (normal, 0-15 mm/hr), while C- reactive protein (CRP) was abnormally elevated in 56 out of 80 (58.3%) patients (normal, 0-3 mg/L).

Induction of remission was achieved in 80 (83%) patient using oral prednisolone in a dose of 1-2 mg/kg/day (maximum 40 mg/day) for 4 weeks followed by a gradual reduction of the dose for 4-8 weeks depending on the response. Remission was successfully induced using only enteral nutrition in 16 of 50 patients in whom this modality of therapy was attempted. Enteral nutrition was given as liquid polymeric formula for 6 weeks followed by gradual and slow introduction of solid food. These formulas were delivered through a nasogastric tube in 13 patients and orally in 3 patients.

Azathioprine was used for maintenance of remission in almost all patients in addition to 5-amino salicylic acid derivatives (mesalazine). The usual dose for azathioprine was 2-2.5 mg/kg/day, while the dose for mesalazine was about 50-100 mg/kg/day as tolerated. Thirty patients required biological therapy using infliximab (n=22) or adalimumab (n=8). Patients who were candidates for biological therapy were routinely screened for TB using the tuberculin skin test and a chest x-ray. Also, prior to treatment, they were screened for hepatitis B and C viruses and HIV.

Infliximab was given as intravenous infusion in a dose of 5 mg/kg/dose at 0, 2 and 6 weeks for induction followed by treatment every 8 weeks as maintenance. Adalimumab was given subcutaneously in a dose of 80 mg initial followed by 40 mg every other week for younger children or at the initial dose of 160 mg followed by 80 mg every other week for adolescents. Patients were evaluated after 12 months of treatment and a decision was made with the family whether to continue or to stop treatment at that stage. The indications for biological therapy in this cohort were 1) perianal and fistulizing disease, 2) failure of conventional treatment using azathioprine and 5-aminosalysylate as maintenance therapy with frequent relapses requiring repeated courses of corticosteroids or 3) extensive disease causing severe growth failure.

Surgery was required for 8 (8.3%) patients. Three had diversion colostomy for severe perianal disease, one had resection of inflammatory mass at the terminal il-

eum and cecum with anastomosis, one had repair of the internal fistula into the urinary bladder, one had repair of a perforated colon, one had drainage of an intra-abdominal abscess, and one had deep gluteal abscess drainage.

The mean (SD) duration of follow up was 3 (2.8) years, range from 0.15 to 12 years. Twenty-nine (30%) patients were lost to follow up. All patients treated with corticosteroids were steroid responsive. Eleven (11.5%) were steroid dependent. Fifty-six (58.3%) patients had one or more relapses during follow up. The median number of relapses per year was 0.67 (range, 0.1 to 6.55 relapses per year).

DISCUSSION

CD is becoming more prevalent than UC with a greater percentage of patients presenting during childhood.[14] In this series, CD comprised 61.5% of the total IBD cases diagnosed during the study period. There was a significant increase in the number of new cases every year as shown in **Figure 1**. This observation confirms a previous report.[11] It is debatable whether this is due to lack of diagnostic facilities and trained medical personnel or whether the disease incidence is truly increasing. It has been suggested that marked socioeconomic development experienced in Saudi Arabia over the years has not only lead to an improvement of health services in general, but also has been associated with a clear change towards a more Westernized lifestyle.

In this study a significant number of patients were infants (**Figure 2**). The development of IBD in infancy is extremely rare. Published data from epidemiological studies and IBD registries in North America and Europe suggest that less than 1% of children with IBD present during the first 12 months of life.[15,16] In contrast to older children, almost all infants with IBD have disease involving the colon. Additionally, there may be a higher prevalence of perianal involvement in this age group.[17]

In line with the high rate of consanguineous marriages in Saudi Arabia,[18] we found a high rate of first-cousin consanguinity in this study. We also found a family history of IBD affecting first-degree relatives in 9 (9.4%) patients. This rate of family clustering with IBD is close to the rate of 10.9% seen in 129 Greek children with CD reported by Roma et al.[19] In our study the concordance rate for the clinical phenotype of the disease was 78%. This is higher than the concordance rate of 58.3% in children with CD reported in the study by Roma et al.[19]

IBD may be complicated by EIMs. Six percent of pediatric patients had at least 1 EIM before diagnosis with IBD. At least 1 EIM will develop in 29% within 15 years of diagnosis.[20] In our cohort oral manifestations were the most common. This frequency is less than the 48% reported in a study from Dublin.[21] The most common lesions found in our study were angular stomatitis and aphthous ulcerations. In another study with Italian adults angular cheilitis was the most frequent oral manifestation,[22] other investigators have reported mucogingivitis and cobblestoning as being the most frequent oral lesions.[21,23] Tongue involvement in CD has been rarely reported as an isolated manifestation,[24] or part of the rare Melkersson-Rosenthal syndrome which is associated with orofacial swelling and relapsing facial paralysis.[25] Our patients had isolated tongue involvement with deep ulcerations with loss of tissue causing irregularities at the margins of the tongue that healed after treatment with immunosuppressive therapy.

Liver involvement in the form of type-1 autoimmune hepatitis occurred in two (2%) patients. Nemeth et al[26] reported mild pathological liver function in 4 (33%) of 12 pediatric patients with CD. Also, Hyams et al[27] reported chronic active hepatitis in less than 1% in children with either CD or UC, while sclerosing cholangitis was reported in 3.5% of UC patients and less than 1% of CD patients. None of our patients had sclerosing cholangitis. Both patients described in the current study responded well to treatment with corticosteroids with normalization of their liver function tests and subsequently maintained on low dose of corticosteroids.

The development of stricturing and penetrating disease are among the important complications of CD diagnosed during childhood and adolescence. In our patients stricture complications were associated with small bowel disease in line with other studies.[28,29] However, penetrating complications were not found to be associated with the disease location in contrast to some other investigators who have reported an association between penetrating complications and colonic disease,[30,31] while others reported an association between penetrating complications and small bowel CD.[32,33]

The medical treatment of newly diagnosed CD patients included induction of remission followed by maintenance and prevention of relapse. In addition to corticosteroids, enteral nutrition therapy is established as a valid and effective treatment in pediatric CD. Some studies have shown that enteral nutrition is comparable to corticosteroids in achieving remission.[34] One additional advantage of using enteral nutrition is the induction of mucosal healing.[35,36] In our cohort of children with CD, we were able to use enteral nutri-

tion successfully in only one-third of patients who attempted enteral nutrition. The difficulties encountered in using enteral nutrition were related mainly to compliance, especially in the adolescent age group. Other factors which may have worked against the success of enteral nutrition could have included lack of access to dietetic support and lack of financial support for the provision of such expensive formula.

Biological therapy in the form of anti-tumour necrosis factor alpha (anti-TNF-α) was considered in a selected group of patients with moderate to severe CD, particularly in those with perianal and fistulizing disease in whom other medical therapies were often unsuccessful. Infliximab and adalimumab are the most commonly used anti-TNF-α agents for the treatment of patients with moderate to severe CD.[37-39] In this cohort, 30 children were successfully treated with biological therapy using infliximab or adalimumab.

In conclusion, this study has shown that the clinical characteristics of CD including the disease phenotype and behavior, in children in the Western Province of Saudi Arabia are generally similar to those reported from the Western population. Pediatricians should be aware of various presentations of CD since early recognition of the disease and timely medical treatment helps in achieving control of the disease and avoids its complications.

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