INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder that consists of ulcerative colitis (UC), Crohn’s disease (CD), and indeterminate colitis (IC) and manifests in up to 25% of patients during childhood. The natural history of pediatric IBDs is poorly understood and generally unpredictable and affects several aspects of...
a child's health. In general, natural history can be assessed using variables including disease activity, growth failure, complications, treatment options, and outcome. At present, scanty data is available in our region. Moreover, few studies found significant variation in the demographic distribution, familial predisposition, phenotype, and outcomes of IBD between different ethnic groups, with environmental and genetic factors also playing a role. Although the incidence of IBD, especially CD, has increased in many populations, there is a paucity of studies describing different factors and their role in disease outcome. The aim of this study is to address the various factors affecting disease outcome and to compare the data with international data. Although the limitation of our study is that these variables were assessed at a single point during the disease course, it can be a base for future studies in our area with its peculiarity in ethnicity, environmental, and genetic factors in comparison with studies in European and American nations.

PATIENTS AND METHODS

This is a retrospective study in which the charts of all children less than 14 years of age, diagnosed as IBD and followed up in our hospital (King Faisal specialist Hospital and research center, Riyadh, Saudi Arabia) from January 2001 to December 2011 were reviewed. This study included pediatric patients less than 14 years of age at the time of diagnosis who were diagnosed with IBD confirmed by endoscopic, radiologic, and histopathologic evaluation. Variables included patient demographics (age, gender, nationality, and region), clinical presentation, duration of symptoms before diagnosis, growth, family history, diagnostic findings including laboratory, radiologic endoscopic, and histopathologic findings which were previously published as the first part of our work. In this study, we collected information regarding the extraintestinal manifestations, behavior of IBD, changes in diagnosis, growth failure, complications, and modalities of medical and surgical management, as well as its outcome. The data were analyzed and presented in simple percentage format.

Definition and diagnostic criteria for extraintestinal symptoms

Arthritis was defined as the presence of intraarticular swelling or two or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Peripheral arthritis (not spine) was mostly lower extremities including hips, knees, ankles, feet, and toes. Osteoporosis is a condition characterized by the progressive loss of bone mass and microarchitectural deterioration, leading to increased bone fragility and susceptibility to fractures. Bone mineral density (BMD) and bone mineral content was determined using dual energy X-ray absorptiometry (DXA). Low BMD is expressed as Z-score less than or equal to −2.0. Primary sclerosing cholangitis was diagnosed according to a consistent laboratory test, liver histology, endoscopic retrograde cholangiopancreatography (ERCP) findings, and magnetic resonance cholangiopancreatography (MRCP) findings. Pyoderma gangrenosum and erythema nodosum were diagnosed using characteristic clinical findings. Uveitis/episcleritis were encountered when reported by an experienced ophthalmologist.

Crohn’s disease behavior assessment

We reported disease behavior in CD patient according to The Montreal Classification which defines three behaviors for CD – nonstricturing nonpenetrating disease (B1), stricturing disease (B2), and penetrating disease (B3). We used clinical evaluation and different diagnostic modalities to determine the involvement and assess disease behavior including endoscopic evaluation [Ercp and capsule endoscopy, histological, and radiological tests (gastrointestinal contrast, CT scan, MRI, MRCP)].

Ethical consideration

This study was reviewed and approved by Research Ethics Committee (Research Advisory Council, Office of Research Affairs) at KFSH and RC.

RESULTS

Sixty-six patients were diagnosed with IBD from January 2001 to December 2011; 36 (54.5%) had CD, 27 (41%) had UC, and 3 (4.5%) had IC. We published the initial part of our study on the clinical presentation of IBD as a single center experience in an earlier report. In this second part, we focused on the natural history assessed by growth failure, extraintestinal manifestations, CD behavior, and outcome of medical and surgical management.

Growth failure

Growth failure (defined as height and weight less than the 5th percentile). At the time of diagnosis, growth failure was reported in 17 CD patients (47%) and 5 UC patients (18.5%) while it was found in all IC patients 3 (100%) with total percentage of 37.9% (25 patients) in all IBD.

Extraintestinal manifestation

Extraintestinal manifestations were presented in 32% of all IBD patients (33.3% in both CD and UC, 66.7% in IC). The most common extraintestinal manifestation in CD was peripheral joint inflammation found in 6 (16.7%)
patients followed by osteoporosis and/or osteopenia in 5 (14%) patients whereas sclerosing cholangitis was reported in 1 (2.8%) patient. The most common extraintestinal manifestation in UC was osteoporosis and/or osteopenia in 6 (22.2%) patients followed by primary sclerosing cholangitis in 4 (15%) patients whereas peripheral joint inflammation was found in only 1 (3.7%) patient [Table 1].

Crohn’s disease behavior

We reported disease behavior in CD patients according to The Montreal Classification which defines three behaviors for CD: nonstricturing nonpenetrating disease (B1), stricturing disease (B2), penetrating disease (B3). Nonstricturing nonpenetrating disease (B1) was found in 25 (69.5%) patients, stricturing disease (B2) in 3 (8.3%) patients, whereas penetrating disease (B3) was found in 8 (22.2%) patients.

Change in diagnosis

Change in diagnosis from UC to CD was noted in 5 patients (7.6%). Confirmed diagnosis was made post colectomy and examination of resected tissue or small intestine studies by capsule endoscopy.

Malignancy

No incidence of cancer was reported in our patients either from the disease itself or due to medications till the end of pediatric follow-up age at 14 years.

Outcome of management

Medical management

Among 66 IBD patients, 8 (12%) were off therapy. UC patients were more often off therapy than those with CD (22.2% vs 5.6%). A total of 14 patients out of 66 (21.1%) were steroid dependent. Among those 6 were CD (16.7%), 6 (22.2%) were UC, and 2 (66.7%) were IC. A total of 38 patients received 5-Aminosalicylic acid (5-ASA) (52.8% in CD vs 63% in UC). Administration of immunosuppressants (azathioprine) was reported in a total of 31 (47%) patients, 19 (52.8%) in CD vs 9 (33.3%) in UC. A total of 12 patients (18.2%) received biological agents (infliximab); 10 (27.8%) patients with CD and 2 (7.4%) patients with UC [Table 2].

Surgical management

A total of 15 (22.7%) IBD patients underwent surgical management. Of the children with CD, 10 (27.8%) underwent 1 or more major operations. Of children with UC, 5 (18.5%) underwent 1 or more major intraabdominal procedures, as shown in Table 2. CD patients underwent various surgical procedures including proctocolectomy with end ileostomy (4 patients), subtotal colectomy with ileorectal anastomosis (IRA) (2 patients), total colectomy with ileal pouch-anal anastomosis (IPAA) (1 patient), right hemicolectomy (1 patient), and bowel diversion with ileostomy (1 patient). The duration between the age of diagnosis and the time of surgery ranged from 1 year to 12 years. Table 3 lists the characteristics and indication of operated CD patients. UC patients underwent either total colectomy with IPAA or proctocolectomy with end ileostomy. Indication of surgery were failure of medical therapy, complication from disease or medication and poor compliance. The duration between the age at diagnosis and time of surgery ranged from 4 years to 10 years and 8 months [Table 4].

DISCUSSION

The natural history of pediatric IBDs is poorly understood and generally unpredictable and affects several aspects of a child’s health. Growth failure in our patients was evaluated using height and weight below the 5th percentile. Growth was more affected in CD patients than UC patients (47% vs 18.5%) in our cohort. Such a finding was reported for CD in different international studies. Growth failure at the time of diagnosis of CD ranged between 10% and 56%.[5,6,12] In UC, growth failure at diagnosis ranged from 0% to 10%. [5,6,12] Our UC patients had higher growth failure in comparison to the international data while it was less in comparison to recent national data.[13]

At least one extraintestinal manifestation is seen in approximately 25–47% of adult patients with IBD.[14,15] In recent studies, extraintestinal manifestations were reported in 2–29% of pediatric patients.[17] The rate was
higher when osteopenia and growth delay were included as an extraintestinal manifestation.\textsuperscript{[18,19]} Extraintestinal symptoms were more frequent in CD than in UC. Our data is not different from international data, although we report similar rate of extraintestinal manifestations in both CD and UC (33%) taking into account that osteopenia was considered an extraintestinal manifestation. If this were to be excluded then the rate of extraintestinal manifestations would be 19.4% and 11.1% for CD and UC, respectively, which is comparable to international data.

Change in diagnosis from UC to CD has been reported in many studies.\textsuperscript{[8]} This was attributed to multiple reasons including improvement in the diagnosis of CD over time as a result of new modalities such as capsule endoscopy, progression of disease during follow-up, and confirmation of histopathology of resected bowel. In our study, change in diagnosis from UC to CD was found in 5 patients (7.6%). Although we had small number of IC patients, none of them were reclassified during follow-up. Mamula et al. demonstrated that in 15% of patients the IBD diagnosis was changed during the course of the illness.\textsuperscript{[20]} Other studies have also reported reclassification from IC.\textsuperscript{[21,22]}

Steroid dependency in our studies was 21% which is almost similar to those reported in pediatric patients in other studies.\textsuperscript{[23,24]} 5-ASA is the most common drug therapy and its use for UC has been reported to be higher.\textsuperscript{[26]} Use of biological medication was reported in 52.8% of CD patients and 33.3% of UC patients. Vernier-Massouille \textit{et al.} reported similar rate for CD (59%) but higher than ours for UC (51%).\textsuperscript{[25]} Use of biological medication was reported in 27.8% and 7.4% for CD and UC patients, respectively, which is almost the same rate as that of a local study (28% and 8%)\textsuperscript{[23]} and other international studies for CD,\textsuperscript{[25]} although its use for UC has been reported to be higher.\textsuperscript{[26]}

There are no clear universal guidelines for medication withdrawal in IBD patients. Therefore, it is essential to identify patient groups where the maintenance therapy

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### Table 3: Characteristics of operated CD patients

| Operation | Indication | Sex | Age at Dx (years) | Age at operation (years) | Other surgery (age at operation in years) |
|-----------|------------|-----|-------------------|--------------------------|-------------------------------------------|
| Bowel diversion with ileostomy | Severe perianal disease | F | 0.75 | 2 | Bowel perforation post colonoscopy (6) |
| Ileocecal resection | TI stricture | M | 13.33 | 17.6 | N/A |
| Subtotal colectomy with IRA | Failure of Medical Rx Steroid Dependent Fistulizing Disease Failure of medical treatment | F | 6.08 | 18.25 | 20.33 |
| Proctocolectomy with end-ileostomy | Failure of medical treatment Fistulizing disease Defunctioning ileostomy Extensive perianal disease Failure of medical treatment Extensive perianal disease | F | 11.4 | 23.17 | 5 |
| Total colectomy with IPAA | Failure of medical treatment Failure of medical treatment | M | 10.33 | 14.25 | N/A |
| Rt Hemicolectomy | Failure of medical treatment | M | 13.33 | 14.33 | Appendectomy |

Dx: Diagnosis, N/A: Nonapplicable, IPAA: Ileal pouch-anal anastomosis, IRA: Ileorectal anastomosis, TPN: Total parenteral nutrition, TI: Terminal ileum

### Table 4: Characteristics of operated UC patients

| Sex | Age at Dx surgery | indication | Age at surgery | Other surgery | Complication |
|-----|-------------------|------------|----------------|----------------|--------------|
| M   | 7 y 4 m Total colectomy with IPAA | Failure of medical treatment | 12 y 2 m | N/A | Growth failure osteopenia |
| Fe  | 3 y 6 m Total colectomy with IPAA | Sever UC Steroid dependent Poor compliance | 14 y 2 m | N/A | Growth failure |
| Fe  | 8 y 2 m Total colectomy with IPAA | Poor compliance Experience of family with another sibling | 14 y 3 m | N/A | Growth failure |
| M   | 8 y 2 m Total colectomy with IPAA | N/A | 12 y 2 m | N/A | Reduction of intussusceptions, resection of distal AC, TC, and colostomy Adhesion lysis (8 m and 3 y postsurgery) Anal dilatation (3 y postsurgery) |
| Fe  | 8 y Proctocolectomy with end ileostomy | N/A | 14 y 4 m | N/A | Intussusceptions Short stature Intestinal obstruction |

Dx: Diagnosis, AC: Ascending colon, TC: Transverse colon, N/A: Nonapplicable, IPAA: Ileal pouch-anal anastomosis, UC: Ulcerative colitis
can be discontinued without a high risk of relapse. The discontinuation of therapy should be considered only in patients who have a milder disease course and who are in a complete remission with no alterations in laboratory parameters and with a negative colonoscopy.\textsuperscript{[27-28]} Taking this into consideration, we were able to discontinue medication in 12% of our IBD patients.

Surgery plays an important role in the management of pediatric IBD patients. The most common indication of surgery in the pediatric age group is failure of medical therapy to control the disease activity. Other indications include complication of the disease such as obstruction or fistulas, unacceptable side effects of medication, and growth failure. Cancer is a rare indication in children.\textsuperscript{[30]} The aim of surgery is to control disease progression, manage complication, and improve growth and nutrition. Although some extraintestinal manifestations are improved by surgery, some are not.\textsuperscript{[31]} Colectomy rates in UC at five years from diagnosis range between 14%\textsuperscript{[32]} and 24%\textsuperscript{[33-35]} in children. Surgical resection requirement in CD was 34%–50% at 5 years from diagnosis in pediatric age group.\textsuperscript{[36,37]} IPAA is now the gold standard surgery in UC,\textsuperscript{[38]} while in CD the golden rule is to resect only symptomatic macroscopic disease.\textsuperscript{[39]} Our study is not different from international data where the rate of surgery was 22.7% (27.8% in CD vs 18.5% in UC). The most common indication was failure of medical treatment to control disease activity. IPAA was the most common procedure in UC whereas proctocolectomy with end-ileostomy is the most common in CD.

**CONCLUSION**

Many issues in pediatric IBD can directly or indirectly affect the natural history of diseases. Although our study is similar to international studies, the timing was specific, at initial presentation or at the time of data collection. Hence, more studies are needed in our area focusing on multiple factors affecting the natural history and disease progression as well as the change in these factors during the disease course.

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**Conflicts of interest**

There are no conflicts of interest.

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