Ulcerative colitis in children and adolescents from the Western Region of Saudi Arabia

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ABSTRACT

الأهداف: وصف النمط السريري لدى الأطفال والمراهقين المصابين بالتهاب القولون التقرحي في مستشفى جامعة الملك عبدالعزيز بجدة، المملكة العربية السعودية.

الطريقة: أُجريت هذه الدراسة الاسترجاعية التي شملت الأطفال والمراهقين المصابين بالتهاب القولون التقرحي في مستشفى جامعة الملك عبد العزيز بجدة، المملكة العربية السعودية، واستمرت خلال الفترة من يناير 2001م إلى مارس 2010م. لقد قمنا بجمع المعلومات السريرية والديموغرافية من سجلات المرضى، ونتائج التنظير والفحوصات.

النتائج: شملت الدراسة 57 مريضاً مصاباً بالتهاب القولون التقرحي حيث كان متوسط العمر عند التشخيص 8.8 عاماً والانحراف المعياري 4.9 عاماً. وقد كان عدد الإناث 54 بما نسبته 59.6%، وعدد الذكور 42 بما نسبته 73.7%. وتمثلت أكثر الأعراض الشائعة بين المرضى فيما يلي: آلام البطن (93%)، ونزيف الشرج (93%)، والإسهال (86%). كما شكلت نسبة المظاهر المعوية الخارجية 7% من المرضى، و كان وجود التاريخ الأسري بأمراض الأمعاء الالتهابية لدى الأقرباء من الدرجة الأولى إيجابياً عند 2 من المرضى حيث شكل ما نسبته 3.5%. وبتحديد مدى اتساع التهاب الغشاء المخاطي بالتنظير فقد كان مدى الالتهاب حاداً عند 77.2%، وفي الجزء الأيسر من القولون عند 12.3%، وفي الطرف البعيد للقولون بنسبة 10.5%. كما صُنفت درجة التهاب الغشاء المخاطي عند التقييم عن طريق المنظار من متوسطة إلى حادة. وبدراسة النمط السلوكي للمرض فقد كان هناك أنماط متعددة وهي: النمط المزمن المتعدد الانتكاسات (50.9%)، والنمط الخالي من الانتكاسات (40.4%)، والنمط المزمن المستمر مع حدوث تفاقم متكرر (8.8%). كما أظهرت النتائج المخبرية حدوث فقر دم عند 86% من المرضى، وارتفاع عدد الصفائح الدموية عند 74.4%، ونقص ألبومين الدم عند 54.4%، وارتفاع معدل ترسيب كريات الدم الحمراء عند 83%، وارتفاع نسبة بروتين ج التفاعلي عند 77.8% من المرضى.

خاتمة: أثبتت الدراسة بأن الخصائص السريرية لالتهاب القولون التقرحي مشابهة عموماً لما ورد في التقارير الغربية المنشورة سابقاً، وهكذا فإنه يجب على أطباء الأطفال الإلمام بخصائص المرض، مع الإحالة المبكرة إلى المراكز المتخصصة من أجل تجنب التأخير في التشخيص و حدوث المضاعفات.

Objectives: To examine the clinical pattern of pediatric ulcerative colitis (UC) at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia.

Methods: In this retrospective study, we collected data from the medical and endoscopy records of pediatric ulcerative colitis patients between January 2001 and March 2010. The study took place in the Department of Pediatrics, Faculty of Medicine and King Abdul-Aziz University Hospital, King Abdul-Aziz University, Jeddah, Kingdom of Saudi Arabia.

Results: Fifty-seven patients were investigated with mean age±SD at diagnosis of 8.8±4.9 years. The study population comprised of 54 (59.6%) females and 42 (73.7%) males. The most common symptoms identified were abdominal pain (93%), rectal bleeding (93%), and diarrhea (86%). The extra-intestinal manifestations were observed in some patients (7%), and 2 (3.5%) had family history of first-degree relatives with inflammatory bowel disease (IBD). The anatomical extent of UC was severe in 77.2%, left sided in 12.3%, and distal in 10.5%. The endoscopic assessment of mucosal inflammation was graded as moderate to severe. The disease pattern included chronic relapse type (50.9%), initial onset type (40.4%), and chronic continuous type with intermittent exacerbation (8.8%). Laboratory results demonstrated the following symptoms such as anemia (86%), thrombocytosis (74.4%), hypoalbuminemia (54.4%), high erythrocyte sedimentation rate (83%) and high C-reactive protein (77.8%).

Conclusion: The incidence of UC in the western region of Saudi was found to be similar with reports from the Western population. Pediatricians should be conscious of such manifestations with early referral to specialized centers in order to avoid unnecessary delay in diagnosis and complications.

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Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which consists of ulcerative colitis (UC) and Crohn's disease (CD). The underlying etiology and pathogenesis of IBD remain unknown; however, other studies have shown that it could result from an interaction between genetic susceptibility, environmental factors, and the host immune response. Inflammatory bowel disease has been regarded as a disease primarily occurring in Western populations. Studies have reported high prevalence rates from North America, United Kingdom, and Northern Europe.[1,2] Originally, it was reported that UC is rare or non-existent in Saudi Arabia.[3] However, recently many studies were published indicating the incidence of UC in adults in different regions including both urban and rural areas.[4,5] The first reported UC was in a child in 1989 by El Mouzan et al.[6] This was followed by an epidemiological study of 50 children with IBD from the Central region of Saudi Arabia with 24 children less than 18 years of age.[7] The reason for the increase in incidence of IBD in Saudi Arabia is probably multi-factorial, and may at least partly be related to economic development and change in dietary habits.[8] The aim of this study is to examine the clinical pattern in children and adolescents with UC at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia.

Methods. A retrospective study of all children and adolescents with UC diagnosed at King Abdul-Aziz University Hospital between January 2001 and March 2010 was conducted. A list of patients was studied by accessing the ICD-10 codes of the hospital admissions database. The data were augmented with data from endoscopy unit database to ensure that all possible patients during the study period were included. Diagnosis of UC was based on the presence of diarrhea or rectal bleeding for more than 6 weeks and colonoscopic biopsy showing features suggestive of UC.[9] The patients with IBD older than 18 years, immune deficiency with IBD-like features, lymphocytic and collagenous colitis, intestinal tuberculosis and infectious colitis were excluded. Information on the clinical and demographic data of all patients were obtained from the patient's medical records. Additional information related to disease progression and outcome during follow up were also obtained from the patient's charts if available. This study was approved by the Bioethical and Research Committee, Faculty of Medicine, King Abdul-Aziz University, Jeddah, Saudi Arabia and it was conducted according to the principles of Helsinki Declaration.

The anatomical extent of UC was classified based on Montreal classification as distal colitis (limited to the rectum and sigmoid colon), left sided colitis (disease distal to the splenic flexure), or "extensive" colitis (extending proximal to the splenic flexure).[10] Moreover, endoscopic assessment was performed by a single gastroenterologist and was graded on a scale of normal, mild disease (erythema, decreased vascular pattern, mild friability), moderate disease (marked erythema, lack of vascular pattern, friability, erosions), or severe disease (spontaneous bleeding, ulceration) based on Mayo UC endoscopic score.[11]

Statistical analyses were performed using SPSS version 19 software (SPSS, Inc, Chicago, III). Study variables were expressed as mean±SD, percentage of the total for categorical variables, or as median with interquartile range for skewed distributed variables. All statistical analyses utilized a 0.05 level of significance.

Results. Fifty-seven patients (36% of the total IBD cases) were diagnosed with UC from January 2001 to March 2010. The mean age ± SD at diagnosis was 8.8±4.9 years (95% Confidence interval [CI] 7.5-10.2 range, 1.1-17.7 years) and the age distribution is shown in **Figure 1**. Thirty-four subjects (59.6%) were females. Saudi Arabs were 37.7% (n=42) of all patients. The remaining were non-Saudis (9 Arabs and 6 Asians).

Clinical manifestations. The presenting symptoms are shown in **Table 1**. The median duration of symptoms prior to presentation was 6 months (95% CI 6.2-9, range 2-24 months). The most common symptoms in UC were abdominal pain (93%), rectal bleeding (93%), diarrhea (86%), passage of mucus (75.4%), loss of appetite (59.6%), tenesmus (54.4%), and weight loss (19.3%). The extra-intestinal manifestations (EIMs) included osteoporosis (n=2), peripheral arthritis (n=1), erythema nodosum (n=1), and autoimmune hepatitis (n=1). First-cousin type consanguinity was positive in 20 (35%) parents. Family history of IBD was positive in 2 (3.5%) patients. Both patients had a mother with UC. The anatomical extent of UC classifications included extended colitis as the predominant form in 77.2% (n=44) of the patients, left sided colitis in 12.3% (n=7), and distal colitis in 10.5 % (n=6) (**Figure 2**). Thirty-one patients (54.4%) were graded as severe and 26 (45.6%) as moderate UC. The chronic relapse type of UC was the most common (50.8%), followed by the initial onset type (40.4%), and chronic continuous type with intermittent exacerbation (8.8%).

Laboratory manifestations. Forty-nine (86%) patients were anemic at diagnosis with a mean±SD hemoglobin level of 9.4±2 g/dl (95% CI 8.8-10.03).

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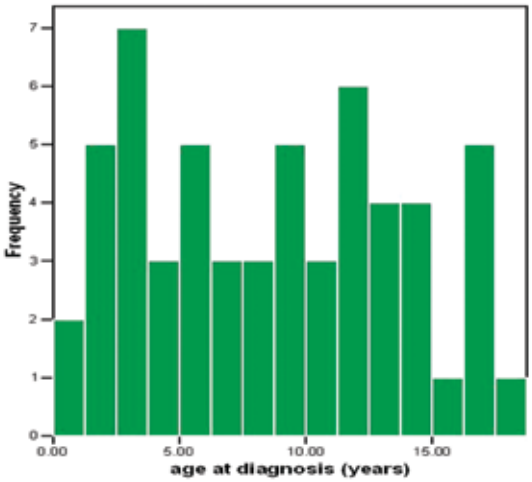

Figure 1 - Distribution of age at diagnosis in 57 patients with ulcerative colitis.

Table 1 - The presenting symptoms in 57 patients with ulcerative colitis.

Symptoms	N	(%)
Abdominal pain	53	(93.0)
Rectal bleeding	53	(93.0)
Diarrhea	49	(86.0)
Passage of mucus	43	(75.4)
Anorexia	34	(59.6)
Tenesmus	31	(54.4)
Weight loss	11	(19.3)
Vomiting	3	(5.3)
Fever	3	(5.3)

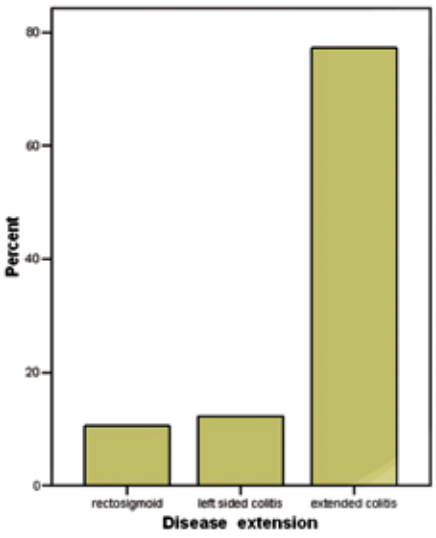

Figure 2 - The classification of the anatomical extent in 57 patients with ulcerative colitis.

Thrombocytosis was found in 27 (74.4%) patients with a mean±SD platelets count of 626±159 (95% CI 563.4-689.5). Thirty-one patients (54.4%) had low albumin with a mean±SD albumin level of 29±4.5 g/l (95% CI 27.6-30.9). Erythrocytes sedimentation rate (ESR) was high in 34 (83%) of 41 patients tested, whilst C- reactive protein (CRP) was positive in 35 out of 45 (77.8%) patients. Logistic regression analysis of the laboratory parameters including hemoglobin level, platelets count, albumin level, erythrocytes sedimentation rate, and C-reactive protein demonstrated that low albumin was independently associated with severe mucosal disease (p<0.001). However, this parameter could not predict the subsequent course of the disease.

Treatments. All patients were administered 5-aminosalyslic acid derivatives (mesalazine) at diagnosis. Forty-three (75.4%) were on corticosteroids and 39 (68.4%) on azathioprine. One patient had bone marrow suppression requiring cessation of azathioprine, and 2 patients had leukocytopenia responded to the adjustment of the azathioprine dosage. Local treatment in the form of corticosteroid and mesalazine enemas was given to 10 (17.5%) patients. Three patients were placed on biological therapy (Infliximab in one and adalimumab in 2) because of persistent symptoms and steroid dependence. However, none of the patients needed surgery.

Discussion. The pathology pattern of UC in the pediatric population is similar to the adult population, which is characterized by diffuse mucosal inflammation limited to the colon and rectum. It may extend proximally in a symmetrical uninterrupted pattern to involve parts or all of the large intestine. The most common symptoms in majority of patient were rectal bleeding and diarrhea. In this study, abdominal pain, bleeding per rectum, and diarrhea were the most common symptoms. Upon diagnosis, children were more susceptible to have severe UC than adults.[12] Only 7% of patients had extra-intestinal symptoms in this study. The extra-intestinal manifestations included osteoporosis in 2 (3.5%), peripheral arthritis affecting the left knee joint in one (2%), erythema nodosum in one (2%), and autoimmune hepatitis in one (2%) patient. In contrast, these symptoms are rare compared to the studies reported from the Western population.[13,14] Furthermore, 68% incidence was reported by Grossman and Debenedetti.[13] Stawarski et al[14] have reported 80% frequency of extraintestinal manifestations (EIMs) in children with UC. However, both groups of investigators demonstrated growth delay as an EIM. A recent multicenter study of a large pediatric IBD registry including 1649 patients reported an incidence of 6% of EIMs.[15] This incidence is similar with the current study,

which is much lower than the reported in the previous 2 studies.[13,14] The rate of first-cousin consanguinity reported in this study was 35%. This consanguinity pattern was only seen in the Saudi patients included in the study, who comprised more than two-third of the patients. This could be explained by the fact that consanguineous marriages being common in Saudi Arabia as reported by El-Mouzan et al.[16] The overall prevalence of consanguinity reported was 56% with the prevalence of the first-degree-cousin being 33.6%. This result is in consistent with the rate reported in our study of 35% for the first-cousin consanguinity. Family history of affected first-degree relatives was positive in 2 (3.5%) male patients. Both had their mothers affected with UC. This rate of first-degree relatives with IBD is lower than the rate of 6.6% of 129 Greek children with UC reported by Roma et al.[17] However, in this study they found a total 100% concordance for UC between index children and their first degree relative, which is consistent with our finding. Ulcerative colitis patients diagnosed at a younger age have severe disease manifestation than patients diagnosed at older age.[18] Epidemiological studies have shown that in 40-50% of adult patients, inflammation is restricted to the rectum or sigmoid colon. In contrast, 25-35% of patients have extended disease or pancolitis.[19,20] With respect to this, pediatric UC has been shown to behave differently. Approximately 60-70% of patients with pediatric onset of UC present with pancolitis, as opposed to approximately 20-30% in adults.[12,21] In this study, children and adolescents with UC, had 77% extended colitis at onset, slightly higher than what has been reported. The severity of the mucosal inflammation as examined by the endoscopy was either moderate in 45.6% or severe in 54.4% cases. In the North Americans, 80% of pediatric UC patients presents with moderate to severe colitis at onset of the disease.[12] They also found that 80% had pancolitis and 80% received corticosteroids within 30 days of diagnosis. These suggest that the severity of the disease in these children with UC may be comparable to that reported from the Western countries. Three patients in this study had biological therapy using anti-TNF-α. The first line of evidence for the potential efficacy of anti-TNF-α therapy in the treatment of UC is the descriptive characterization of high TNF-α production in either the local or systemic level.[22] The second line of evidence comes from animal model of UC that demonstrated beneficial anti-TNF-α treatment effect.[23] Meta analysis of randomized clinical trials showed that infliximab was more effective than placebo for the treatment of moderate-to-severe UC achieving clinical remission in 40% of the patients at approximately 9 months of follow up.[24] It has been suggested that pediatric patients may respond better than adults.[25] Infliximab is usually given by intravenous infusion of 5 mg/kg at 0, 2 and 6 weeks for induction, and every 8 weeks for maintenance therapy. Likewise adalimumab has also been shown to be beneficial in patients with UC.[26] Adalimumab is a fully humanized anti-TNF-α that may be given subcutaneously every other week and is useful in the treatment of refractory pediatric patients with IBD with a remission rate of 61%.[27]

A meta-regression of cohort studies in acute severe UC in Western children showed that 29% of patients failed corticosteroid therapy and require escalation of medical management or colectomy.[28] In another study,[12] 5% of children with UC had to undergo colectomy within a year of diagnosis. None of our patients with acute severe UC or during the course of treatment required colectomy. They responded well to intravenous corticosteroids. This difference in response may be related to differences in gene expression.[29]

The limitations of this study include the lack of detailed analysis of dietary, social and environmental factors that may contribute to the disease process. Data on long term outcome are also missing because some patients either could not be followed up or were transferred to adult care.

The findings of this study should encourage the healthcare decision makers for a National Registry for children and adolescents with IBD. The presence of such registry may open the area for research in order to understand the risk factors, that could contribute to the understanding of the etiology of the IBD in our local population.

In conclusion, UC in children in Saudi Arabia is not uncommon. The clinical manifestations of the disease including site of involvement and disease severity are generally similar to those reported elsewhere. Pediatricians should be aware of this fact to guard against delay in diagnosis. Early identification may help in achieving control with medical treatment, avoiding complications, or requirement for surgery.

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