Extra Intestinal Manifestations in Children with Inflammatory Bowel Disease, A Single Center Report from Iran

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ABSTRACT

Introduction: Inflammatory bowel disease (IBD) is a disorder of unknown etiology categorized into three groups including Crohn disease (CD), ulcerative colitis (UC), and intermediate colitis (IC). In addition to gastrointestinal (GI) symptoms, childhood IBD frequently present with extra GI manifestations. In present study, we aimed to determine extra GI symptoms in children with IBD in Iran.

Methods: Children <18 years old with established IBD diagnosis referred to the Gastroenterology Clinic affiliated with Shiraz University of Medical Sciences during 2007-2017 were included.

Results: Eighty-five children were assessed. CD and UC comprised 26 (30.6%) and 47 (55.3%) of the patients. The mean age was 14.09±2.5 years old with 50% of them were boys. The most frequent presenting complaint was rectal bleeding (37.2%). In patients with CD and UC, 30% and 29% of the patients represented at least one extra GI symptom. The most common extra GI manifestations were growth retardation (11.5%) and arthralgia (7.8%) in children with CD and UC respectively.

Conclusions: Extra GI symptoms are relatively common in children with IBD. Caution should be taken to avoid confusion with other disorders and to timely manage these manifestations.

INTRODUCTION

Inflammatory bowel disease (IBD) is an idiopathic intestinal inflammatory condition. IBD is divided into Crohn’s disease (CD), ulcerative colitis (UC), and intermediate colitis (IC) (1, 2). CD is characterized with intermittent inflammation of gastrointestinal (GI) tract extended from the oral cavity to rectum (3). UC is particularity characterized with rectum involvement extending as continuous superficial GI inflammation. On the other hand, IC is recognized by mucosal inflammation not categorized in neither of the two above-mentioned groups (4).

The global incidence of IBD has been increasing, especially in the young with 25% of newly diagnosed patients aged <20 years old (5, 6). The age of presentation lies with the first years of the second decade of life for both CD and UC. The first peak of CD is the age of 20 with gradually decreasing incidence afterwards until the second peak at 50-70 years (7). UC occurs in a wide range age spectrum; however, the two peaks of incidence are 15-25 and 60 years old with rare reports at <5 years and >75 years old (8).

CD and UC often present with abdominal pain and diarrhea. Rectal bleeding is observed in 83-95% of UC and 13-40% of CD patients (9). Nevertheless, atypical presentations of IBD, known as extra intestinal manifestations (EIM) are especially highlighted in children <18 years old. It has been reported that 17-68% of children with IBD initially present with an extra GI symptom. The most common extra GI manifestations were growth retardation (11.5%) and arthralgia (7.8%) in children with CD and UC respectively. Conclusions: Extra GI symptoms are relatively common in children with IBD. Caution should be taken to avoid confusion with other disorders and to timely manage these manifestations.
cholethiasis, and primary sclerosing cholangitis (PSC) (13, 14). Although the etiology of PSC in the context of IBD is not certain, it has been postulated that aberrant immune reactions and bacteria residing in bile ducts may impart roles in this phenomenon (15). Dermatological presentations have also been noted in 10-15% of patients with IBD (16, 17). Nevertheless, few studies have addressed the frequencies of EIM in children with IBD in Iran. In present study, we aimed to report the distribution and frequencies of these manifestations in children with IBD in Iranian children.

METHODS

All the children with established IBD diagnosis in the Gastroenterology clinic of Shiraz University of Medical Sciences were included. The patients were recruited from 2007 till 2017. Inclusion criteria were the age of diagnosis <18 years old and verified IBD diagnosis based on clinical, endoscopy and histopathological evidences (18).

Clinical and demographic information including present age, the age of diagnosis, gender, vacancy, disease duration, disease subtype (UC, CD, or IC), presenting symptoms, family history of IBD, and finally EIMs (including growth retardation, delayed puberty, oral ulcers, episcleritis, erythema nodosum, arthritis, arthralgia, abnormal liver enzymes, thrombosis, renal dysfunction, PSC) were recorded. The manifestations unrelated to the IBD (for example traumatic joint symptoms etc.) were not considered as EIMs. Also, those patients with incomplete clinical information and unavailable contact numbers to obtain such information (13 out of 98 registered children) were excluded from the final analysis. Statistical analyses were performed in SPSS 16 software.

RESULTS

CD, UC, and IC comprised 26 (30.6%), 47 (55.3%), and 12 (14.1%) of the patients respectively. Family history of IBD was recognized in 4 (4.7%). Only one patient (1.2%) had colectomy. From the total of 85 included children with established IBD, 43 (50.6%) were boys and 42 (49.4%) were girls with the overall mean age of 14.09±2.5 years old. The means of age in boys and girls were 14.39±5.12 and 13.77±5.4 years old respectively. The mean age of diagnosis was 10.53 ± 4.51. The mean duration of IBD was 3.85±3.21 years (Table 1).

The most common clinical symptoms were abdominal pain (65.4%), and diarrhea (59.6%) in children with CD and UC respectively. Clinical presentations in the studied children have been shown in Table 2.

Furthermore, intestinal inflammation (46.2%) and ulcers (34.6%) were most common endoscopic findings in patients with CD and UC respectively (Table 3). Corticosteroids and aminosalicylates comprised the most administered drugs in both CD and UC (Table 4).

The most common EIMs were growth retardation (18.8%), growth retardation and perirectal disease (each 8.3%), and increased liver enzymes (8.8%) in age spectrums of 0-6, 7-12, and 13-18 years old respectively (Table 5).

Table 1. Demographic and clinical findings in children with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Crohn disease N=26 n (%)</th>
<th>Ulcerative colitis N=47 n (%)</th>
<th>Intermediate colitis N=12 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>4.41±12.82</td>
<td>14.79±5.6</td>
<td>5.4±14.19</td>
</tr>
<tr>
<td>Age at Dx (mean, years)</td>
<td>3.78±9.12</td>
<td>4.59±11.03</td>
<td>5.4±11.53</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>(61.5%)</td>
<td>22 (25.9)</td>
<td>5 (5.9)</td>
</tr>
<tr>
<td>Female</td>
<td>(38.5%)</td>
<td>25 (29.4)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>Vacancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>22 (25.9)</td>
<td>26 (30.6)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>Rural</td>
<td>4 (4.7)</td>
<td>21 (24.7)</td>
<td>5 (5.9)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>3.11±3.83</td>
<td>3.5±4.22</td>
<td>1.7±2.65</td>
</tr>
</tbody>
</table>

Table 2. The presenting clinical symptoms in children with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Crohn disease N=26 n (%)</th>
<th>Ulcerative colitis N=47 n (%)</th>
<th>Intermediate colitis N=12 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (n=47)</td>
<td>(17) 65.4</td>
<td>24 (51.1)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Anorexia (n=21)</td>
<td>(5) 19.2</td>
<td>12 (25.5)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Nocturnal diarrhea (n=3)</td>
<td>(0) 0</td>
<td>3 (6.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea (n=50)</td>
<td>(13) 50</td>
<td>28 (59.6)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Fever (n=24)</td>
<td>(10) 38.5</td>
<td>10 (21.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Nausea/vomiting (n=25)</td>
<td>(6) 23.1</td>
<td>15 (31.9)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Weight loss (n=20)</td>
<td>(8) 30.8</td>
<td>7 (14.9)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Rectal bleeding (n=28)</td>
<td>(6) 23.1</td>
<td>18 (38.3)</td>
<td>4 (33.3)</td>
</tr>
</tbody>
</table>
The highest frequencies of EIMs were related to mouth ulcer, growth retardation, and elevated liver enzymes (each with 7%) in males and growth retardation (9.5%) in females. There was no significant difference in the distribution of EIMs between females and males.

In children with CD, growth retardation and mouth ulcer constituted the most observed symptoms (each with 11.5%). In UC, arthralgia was the most common EIM (7.8%, Table 6).

### DISCUSSION

In present study, we assessed the frequencies of EIMs in children with IBD. Overall, in children with CD, growth retardation and mouth ulcer constituted the most observed symptoms (each with 11.5%). In UC, arthralgia was the most common EIM. The most common EIMs were growth retardation (18.8%), growth retardation and perirectal disease (each 8.3%), and increased liver enzymes (8.8%) in age spectrums of 0-6, 7-12, and 13-18 years old respectively. There were no significant associations between the type of IBD or gender with the incidence of a particular EIM.

The frequency of EIM in IBD has been reported from 16-40% (19-22) with musculoskeletal (including arthritis, ankylosing spondylitis) and cutaneous presentations (including erythema nodosum, pyoderma gangrenosum) are among the most common observed conditions reported in as high as 50% of the patients in previous reports (19, 21, 23, 24). EIMs in IBD are associated with significant morbidities and lowering the quality of life status (25). The risk of these EIMs in patients with IBD has been reported as 2.6-29.2 folds higher respective to healthy counterparts. (24) The rate of EIMs...
recurrence has been noted as 13%. (19) Other reported EIMs in IBD include hepatobiliary abnormalities, (26) ocular manifestations, (27) and pulmonary involvement. (28)

Joints are the most common site of involvement in UC reported in 52% of patients (29). This in accordance with our observation as the arthralgia comprised the most common EIMs finding in our UC patients. Genetic and environmental factors are essential for development of UC (30). In addition, females and patients with active disease may be at higher risk of joint diseases (29). In line, both female gender and disease activity have been risk factors of EIMs in patients with IBD (19). The disease activity correlated with intestinal neutrophil activity may predict the development of EIMs in patients with active IBD (31). In fact, higher occurrence of EIMs in post-diagnosis area highlights the role of disease activity in the occurrence of EIMs (32). In addition, lower age of presentation (i.e. childhood IBD) has been associated with higher risk of EIMs (32-34). Nevertheless, we detected no significant deviated distribution of the EIMs among the 0-6, 7-12, and 13-18 age groups. Accordingly, IBD in children <5 years old has shown distinct pathophysiological and clinical features in comparison with IBD presenting within 11-16 years old (19, 35). Oral manifestations (including cobblestoning mucosa, lips, chicks, and gingival involvement) have been reported in 10-80% of patients with CD (36). Overall, 2 out of patients showed erythema nodosum. Therapeutic interventions (i.e. pharmaceutical agents such as TNF antagonists (37) or NSAID and surgical intervention (23, 38) may predispose patients to EIMs. In addition, patients with already developed EIMs may be at higher risk for the emergence of additional manifestations (27). Smoking has been noted as a major environmental contributing factor to EIMs (39). A multi factorial approach including genetic, environmental and immunological factors) has been noted to participate in the development of EIMs in patients with IBD. The role of inflammatory cytokines within GI system may be crucial in this process. (28) In conclusion, EIMs are relatively common in children with IBD. Caution should be taken to avoid confusion with other disorders and to timely manage these manifestations.

CONCLUSION

In conclusion, extra GI symptoms are relatively common in children with IBD. There were no significant associations between the type of IBD or gender with the incidence of a particular EIM. Caution should be taken to avoid confusion with other disorders and to timely manage these manifestations.

REFERENCES


