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Inflammatory Bowel Disease-Experience of a Pediatric Gastroenterology Unit

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Abstract

Inflammatory bowel disease, especially Crohn disease, had increased in the last five decades. We analyzed all the patients of our unit diagnosed with the disease between 2001-2012 but we just considered the patients who respected the Porto criteria to define IBD at presentation. We diagnosed 51 children and adolescents with the disease. Crohn disease was responsible for 62.7% of cases, ulcerative colitis for 31.4% and indeterminate colitis for 5.9%. Considering the 4 different periods of time (2001-2003/2004-2006/2007-2009 and 2010-2012), we observed and increase in the number of cases, but a decrease in the time from onset of symptoms to diagnosis.

Our medical approach with tumor necrosis factor antagonists was reserved for severe disease cases and to spare patients from adverse effects of purine analogues and corticosteroids. Mucosal healing and remission of the disease was achieved in all of the patients under biologic therapy and no serious or life-threating event was reported with their use.

Keywords: Inflammatory bowel disease; Pediatric; Tumor necrosis factor antagonists

Introduction

Inflammatory Bowel Disease (IBD) represents a heterogeneous group of chronic diseases, diagnosed before the age of 20 years in 25% to 30% of cases [1-3]. Recent epidemiological studies have shown an increasing incidence of IBD in the last five decades. Crohn Disease (CD), more than Ulcerative Colitis (UC) and Indeterminate Colitis (IC), is the major responsible for this upraising of pediatric cases [3-6].

The use of biologic therapy (tumor necrosis factor antagonists) is becoming a safe and more advocated strategy to manage pediatric IBD [7-12].

Methods

Retrospective study of the medical patients' files diagnosed with IBD, between 2001-2012, and followed in the pediatric gastroenterology consultation at Hospital de Braga (HB). ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) established the Porto Criteria in July 2005. The recommendations include: total colonoscopy with ileal intubation; upper endoscopy; multiple biopsies and complete small bowel exploration. In our study, four different periods of time were analyzed: 2001-2003/2004-2006/2007-2009 and 2010-2012. We just considered the patients who respected the Porto Criteria to define IBD [2]. The patients diagnosed before July 2005 that completed the recommendations during the evaluation were included.

The following variables were studied: characterization of IBD, sex, family history, age at diagnosis, time from onset of symptoms to diagnosis, clinical presentation, extra intestinal manifestations, laboratory data and treatment options. Endoscopy with multiple biopsies for histology was performed to differentiate CD from UC and determine the extent of inflammation.

Results

IBD was diagnosed in 51 children and adolescents, between 2001-2012 at Hospital de Braga. CD was responsible for 62.7% (n=32) of cases, UC for 31.4% (n=16) and IC for 5.9% (n=3) (Table 1). The three patients with IC were younger than 10 years old. The patients' gender (♂/♀) distribution per type of IBD was the following: CD (20♂/12♀), UC (5♂/11♀) and IC (2♂/1♀). The age at diagnosis varied between 6 and 17 years of old, with a median age of 12 years. Family history of IBD was present in 17.6% (n=9) children. CD was present in six family members and UC in three.

The periods of times between 2007-2009 and 2010-2012 were the periods with more diagnosed cases, but they corresponded to the periods when the time from onset of symptoms to diagnosis was shorter, even if this difference was not statistically significant (ρ>0.01); However the gastroenterology unit, had a relatively constant mean number of consultations every 2-3 months to achieve diagnosis (Table 1).

The symptoms at time of presentation were variable, with abdominal pain present in 82.3% (n=42) of patients, diarrhea in 62.7% (n=32), hematoquezia or rectal bleeding in 35.3% (n=18), weight loss in 25.5% (n=13), lethargy in 23.5% (n=12), anorexia in 17.6% (n=9), fever in 9.8% (n=5), nausea or vomiting in 7.8% (n=4) and oral ulcers in 1.9% (n=1).

Extra intestinal manifestations were reported in 21.6% (n=11) of patients (Table 2).

The extent of inflammatory disease was determined and ileocolitis

Patients/periods of time	2001-2003	2004-2006	2007-2009	2010-2012
CD (n=32)	12.5%	12.5%	34.4%	40.6%
UC (n=16)	0%	43.8%	37.5%	18.8%
IC (n=3)	0%	0%	66.7%	33.3%
Mean time to diagnosis (months): ρ=0.213	11.5	7.5	5.1	3.1
Mean number of consultations to diagnosis	1.75	2	1.47	1.53

Legend: CD (Crohn Disease); UC (Ulcerative Colitis); ID (Indeterminate Colitis)

Table 1: Number of patients diagnosed with IBD per period of time.

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Extra intestinal manifestations (n=11)	CD (n=8)	UC (n=3)
Arthritis	62.5%	33.3%
Episcleritis	25%	0%
Autoimmune thyroiditis	12.5%	0%
Primary sclerosing cholangitis	0	33.3%
Autoimmune hepatitis	0	33.3%

Legend: CD (Crohn Disease); UC (Ulcerative Colitis)

Table 2: Number of extra intestinal manifestations among our IBD patients.

Treatment of acute flares Induction of remission	CD n=32	UC n=16	IC n=3
Aminosalicylates	0%	31.3%	66.7%
Corticosteroids	96.9%	12.5%	33,3%
Aminosalicylates and Corticosteroids	3.1%	56.3%	0%
Anti-TNF agents	6.3%	0%	0%

Legend: CD (Crohn Disease); UC (Ulcerative Colitis); ID (Indeterminate Colitis) Anti-TNF (antitumor necrosis factor)

Table 3: Therapy used for treatment of acute flares and to induce remission.

Prevention of acute flares Maintenance of remission	CD n=32	UC n=16	IC n=3
Aminosalicylates	0%	56.3%	100%
Immunomodulators (azathioprine/methotrexate)	93.8%	43.8%	0%
Anti-TNF agents (infliximab/ adalimumab)	34.4% 6.3% (only anti-TNF)	18.8%	0%

Legend: CD (Crohn Disease); UC (Ulcerative Colitis); ID (Indeterminate Colitis) Anti-TNF (antitumor necrosis factor)

Table 4: Therapy used for prevention of acute flares and maintenance of remission.

was the most frequent type in CD. It represented 84.4% (n=27) patients. Isolated terminal ileum inflammation was present in 9.4% (n=3) CD patients and colitis in 6.2% (n=2). Upper endoscopy found giant cell granulomas and aphthoid ulcers in 15.6% (n=5) CD patients, even if only three of these had upper gastrointestinal symptoms. Gastritis was detected in 25% (n=8) and anal disease was present in 25% (n=8) CD patients.

In the group of UC, pancolitis was the most prevalent type, with 87.5% (n=14) patients, followed by distal colitis in 12.5% (n=2). Proctitis was not present in our UC group and backwash ileitis was diagnosed in 18.8% (n=3) of patients.

Reduced level of hemoglobin (Hb<11.0 g/dl) was present in 39.2% (n=20) patients, eleven of them with CD and nine with UC. Raised markers of inflammation (erythrocyte sedimentation rate, C-reactive protein) were present in 86.3% (n=44) of patients. Ferritin level at presentation was checked in 29 children and it had a value <15 ng/ml in 24.1% (n=7), two of them with CD, four with UC and one with IC. IgA or IgG anti-Saccharomyces cerevisiae antibodies (ASCA) were positive in 46.9% CD patients and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) in 6.3% UC patients. In CD patients, (ASCA+/pANCA-) presented a sensitivity and specificity of 57.7% and 93.8%, respectively. The combination of (ASCA-/pANCA+) displayed sensitivity of 25% and specificity of 100% for UC diagnosis.

The medical treatment, besides the symptomatic and supportive therapy, to induce remission depended mainly on the use of corticosteroids (Table 3). The prevention of disease flares was achieved in our pediatric population with the use of azathioprine in the majority of CD patients and with an almost equivalent use of aminosalicylates and immunomodulators in UC patients (Table 4). Methotrexate was used only in a CD adolescent with polyarticular Juvenile Idiopathic Arthritis (JIA).

The management with biologic agents to maintain remission was performed in 27.5% (n=14) patients, twelve of them were under infliximab periodic infusions and the other two were submitted to adalimumab therapy (Table 4). We do report four hypersensitive reactions to infliximab periodic infusions controlled with acetaminophen and antihistamic therapy.

A step-up medical approach was conducted in the majority of our patients, with the exception of two severe disease cases where we preferred an earlier use of anti-TNF (antitumor necrosis factor) agents to induce and maintain remission (Tables 3 and 4). The two cases corresponded to two fistulizing CD patients. The other 12 cases that needed biologic therapy were previously under azathioprine, but eight of them did not achieve remission with the purine analogue and four developed side effects. We report two patients with gastrointestinal side effects (nausea and vomiting), one patient with anemia and another one with acute pancreatitis attributable to azathioprine.

Surgical management after the diagnosis of IBD was needed in two patients with CD. A fistulectomy was done to a patient with severe anal disease and an ileal resection was performed in one of the patients with fistulizing disease.

Discussion

We detected an increase of IBD cases during the period of 2001-2012, with a significant increase of CD. This type was more frequent in boys and UC was more prevalent in girls.

Considering the different periods of time, we can say that the unit progressively diagnosed more cases and that the time to achieve diagnosis was shorter. This could be due to an increase of experience of the members but also to the scientific reunions and formation meetings that the unit gave to general practitioners who are responsible for the referring of patients. In our opinion, we verified an increase of knowledge about pediatric IBD among the medical community of our region, reflected in a shorter time to achieve diagnosis and at the same time an equivalent mean number of consultations of the gastroenterology unit.

The periods of times between 2007-2009 and 2010-2012 were the periods with more diagnosed cases, but they corresponded to the periods when the time from onset of symptoms to diagnosis was shorter, even if this difference was not statistically significant ($\rho>0.01$); However the gastroenterology unit, had a constant mean number of consultations every 2-3 months to achieve diagnosis.

Abdominal pain was the most frequent complain of our group of patients and arthritis was our most common extra intestinal manifestation. Ileocolitis and pancolitis were the most common forms of CD and UC respectively.

Corticosteroids were the drugs of choice, in the majority of cases, to induce remission of bowel inflammation and azathioprine the most chosen therapy to maintain remission and prevent flare ups. Our medical approach with anti-TNF agents was reserved for the most severe cases, to maintain remission after azathioprine failure and to spare the patients to some adverse effects of purine analogues and to stop corticosteroids. We do not report any serious or life-threating event with the use of biologic agents.

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