Putowski Maciej, Padala Olga, Krupa Adrianna, Konopelko Michal, Piasek Ewa, Mazurek Marek. Inflammatory bowel disease in children. Journal of Education, Health and Sport. 2019;9(8):406-411. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3379040
http://ojs.ukw.edu.pl/index.php/johs/article/view/7327

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.08.2019. Revised: 15.08.2019. Accepted: 27.08.2019.

Inflammatory bowel disease in children

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Abstract

Pediatric inflammatory bowel diseases (IBDs), including Crohn disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory disorders of the gastrointestinal tract. The incidence and prevalence of IBD is increasing, and approximately 25% of all patients are diagnosed before the age of 18 years. The pathogenesis of IBD is not fully understood but is thought to be mediated by dysregulated mucosal immune response, microbial dysbiosis, genetic and environmental factors. The presentation of IBD, especially in children and adolescents is variable, including both gastrointestinal and extraintestinal manifestations.

The recommended diagnostic procedures of choice are ileocolonoscopy and esophagogastroduodenoscopy. IBD are diagnosed by the combination of clinical, pathological, endoscopic and serological features.

The aims of therapy in pediatric IBD is to induce and maintain clinical remission, relieve symptoms, optimize growth, improve quality of life, and minimize toxicity as much as possible. The ECCO/ESPGHAN consensus guidelines include exclusive enteral nutrition, corticosteroids, 5-aminosalicylates, immunomodulators, biologics and surgery.

Key words: inflammatory bowel disease, Crohn disease, ulcerative colitis

Epidemiology

Pediatric inflammatory bowel diseases (IBDs), including Crohn disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory disorders of the gastrointestinal tract. The incidence and prevalence of IBD is increasing, and approximately 25% of all patients are diagnosed before the age of 18 years [1]. Among all children and adolescents with IBD approximately one-quarter of them are under the age of 10 years at diagnosis [2]. In Poland, the annual incidence of IBD in the population of children under 15 years of age is about 2.8 per 100 000 [3].

Crohn Disease and Ulcerative Disease

Both CD and UC are characterized by the chronic inflammatory process in the gastrointestinal tract. In CD, it can affect any part of the digestive tract from the mouth to the anus, however lesions are located most often in the final section of the small intestine. Inflammation reach through whole thickness of gastrointestinal track and damaged areas appear next to areas of healthy tissue. On the other hand, in UC, the inflammatory process is located initially in the rectum, but may spread proximally to different lengths, including the entire colon and affects only the mucous membrane [4]. Despite differences in clinical manifestation, histopathology and pathogenesis, the treatment is similar in both diseases.

Pathogenesis

The pathogenesis of IBD is not fully understood but is thought to be mediated by dysregulated mucosal immune response, microbial dysbiosis, genetic and environmental factors [5]. More than 200 genes that are associated with development of IBD. These genes, involved in innate and adaptive immunity or epithelial function, play key role in immune homeostasis [6]. Dysregulated immune response to intestinal microbiome in refer to genetic predisposition is thought to be the trigger for chronic inflammation [7]. Numerous environmental risk factors have been identified in pathogenesis of IBD such as diet, antibiotic use, lack of breastfeeding, a rising incidence of IBD over the last few decades and higher prevalent in developed countries [8-9]. There is also confirmed that dysbiosis is closely linked to initiation or progression of IBD, however it is whether dysbiosis is a primary or secondary

event [10]. Among bacteria, pathogenic Escherichia coli, Bacteroides vulgatus and Desulfovibrio desulfuricans are indicated as involved in inflammation process of IBD [11].

Symptoms

The presentation of IBD, especially in children and adolescents is variable. Manifestation of the disease include both gastrointestinal and extraintestinal symptoms. The symptoms are consistent and are results of inflammation in the gastrointestinal tract. The typical presentation of UC is commonly abdominal pain and bloody diarrhea, often with frequent bowel movements at night. The onset of symptoms in UC is generally more acute that CD, thus infective colitis by stool culture should be taken in the consideration in the different diagnosis. The presentation of Crohn's disease is more varied and sometimes subtle. It can be characterized by bloody diarrhea and abdominal pain as well as non-bloody diarrhea, weight loss, growth retardation, malaise, fatigue, anemia, or fever [7]. The presentation of the disease is associated with localization of the gastrointestinal occupation. Children with CD affecting the mid-gut experience intermittent abdominal pain, weight loss and disturbances of bowel habit. If disease is localized in the colon experience, symptoms are similar but rectal bleeding is more likely to occur. IBD may be also manifested by fistula, anal canal stricture, or abscess [12].

Extraintestinal manifestations may be the initial presentation of IBD and are more common in Crohn's disease than in ulcerative colitis. The most common extraintestinal manifestation of IBD in children and adolescents is impaired growth which occurs in 10 to 30% of cases. Approximately 10% of pediatric patients have other extraintestinal manifestations of IBD at diagnosis [13]. Extraintestinal symptoms can involve dermatologic, musculoskeletal, hepatic, ophthalmologic, renal, pancreatic, or hematologic systems, i.e. erythema nodosum, pyogenic granuloma, uveitis, episcleritis, arthritis, and primary sclerosing cholangitis. Up to 35% patients with IBD have extraintestinal manifestations. Moreover, anemia occurs in two-thirds of pediatric IBD patients [12,14]. In some rare cases, patients may be diagnosed with peritonitis, small bowel obstruction, appendicitis, or other surgical emergencies [15].

Diagnosis

The diagnostic evaluation in a patient suspected of having IBD is to investigate all medical history including symptoms, coexisting diseases and course of the disease. A complete physical examination should be performed, including skin, oral and perianal inspection and assessment of height and weight using percentile curves as well as pubertal development [16]. Initial test should include a complete blood count, liver enzymes, albumin, ferritin, C reactive protein (CRP), erythrocyte sedimentation rate (ESR). Test have a role in investigation but are not diagnostic. Furthermore, fecal markers such as calprotectin correlates significantly with mucosal inflammation in IBD. Stool sample analysis should include culture and sensitivity, ova and parasites, and C. difficile toxin to exclude enteric infection [7, 15].

In 2005, the IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published the Porto Criteria guidelines on the diagnostic workup for PIBD, which were revised in 2014. The recommended diagnostic procedures of choice are ileocolonoscopy and esophagogastroduodenoscopy in suspected cases of IBD. Multiple biopsies should be obtained from all sections of the visualized gastrointestinal tract, even in the absence of macroscopic lesions. Ileocolonoscopy plays crucial role in diagnostic in pediatric IBD. According to guidelines, IBD are confirmed by the combination of clinical, pathological, endoscopic and serological features [17,18].

Treatment

The aims of therapy in pediatric IBD is to induce and maintain clinical remission, relieve symptoms, optimize growth, improve quality of life, and minimize toxicity as much as possible.

Moreover, achieving mucosal healing may result in changing the natural history of the disease and decrease the need for surgery due to complications such as progressive bowel destruction and increased risk for colorectal cancer [19]. There is ECCO/ESPGHAN consensus guidelines for the medical management of pediatric IBD [20].

Exclusive Enteral Nutrition (EEN)

First-line treatment to induce remission in children and adolescents with Crohn's disease is exclusive enteral nutrition (EEN) defined as the provision of essentially 100% of caloric needs by liquid formula. Duration of EEN therapy typically is 8 to 12 weeks. Several studies have showed that EEN has similar efficacy to corticosteroids in the induction of remission. However, EEN has beneficial effect on growth and was shown to be superior to corticosteroids alone in treatment of active disease when the primary outcome was mucosal healing [21,22].

Corticosteroids

Corticosteroids should be used only for induction of remission. Oral corticosteroids are recommended as first line treatment in UC, when activity of the disease is high, or the disease is severe and also in inducing remission in children with moderate to severe CD if EEN is not an option [23]. Patients on steroid therapy require regular observation for potential adverse side-effects during long term use. Budesonide is a specific corticosteroid that undergoes extensive first-pass metabolism in the liver. Different available formulations of budesonide can be beneficial for induction of remission with lower systemic bioavailability and side effects, however it is not as effective as conventional corticosteroids [24].

5-aminosalicylates

Oral 5-aminosalicylates (5-ASAs) can be used for induction of remission in mild to moderate as well as maintenance of ulcerative colitis. They can be also administered topically via enema or suppository. Sulfasalazine whas the first 5-ASA used for more than 40 years to treat IBD, but many patients suffered from adverse effects such as nausea, headache, fever, and rash. Newer sulfa-free 5-ASA i.e mesalamine, balsalazide disodium, are characterized with improved drug tolerance. 5-ASA drugs are still commonly prescribed for CD, however there is no strong evidence supporting their efficacy. Paradoxical exacerbation of colitis, interstitial nephritis, pericarditis, and pneumonitis are rare adverse effects of 5-ASAs [25].

Immunomodulators

Immunomodulators, such as thiopurines and methotrexate, are used mainly as maintenance therapy of IBD. These drugs have delayed onset and their effect may take two to three months to be optimal. Adverse effects associated with thiopurines include myelosuppression, hepatotoxicity, and pancreatitis [26].

Biologics

Anti-TNF treatment is recommended as induction and maintenance therapy in severe IBD or when patient did not respond to previous therapies. Biological therapy should by first choice for patients with perianal fistulizing disease, growth failure, or extraintestinal manifestations. Combination therapy with immunomodulators and anti-TNF was found to

increase the chance of 5-year benefit from infliximab [7]. Vedolizumab has been shown to result in clinical response and remission in IBD patients [27].

Surgery

Despite medical advances, surgical intervention is still part of management of IBD. In children with UC refractory to medical therapy, total colectomy with ileal pouch anal anastomosis is indicated. Up to 26% of children with UC will need a colectomy in the first five years from diagnosis [28]. In CD, surgery may be performed due to complications such as fistulas, intra-abdominal abscesses, and bowel strictures or be an option to induce remission of localized disease.

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