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Extradigestive manifestations of IBD in pediatrics

M. ALOI, S. CUCCHIARA

Pediatric Gastroenterology and Hepatology Unit, Department of Pediatrics, University "La Sapienza", Rome (Italy)

Abstract. – Inflammatory bowel diseases (IBD) are often associated with extraintestinal manifestations (EIMs), which occur in approximately one third of patients. There is only few published data on the occurrence of these manifestations in children and adolescents, so most of the data are taken by studies in adult patients. The organs most commonly affected are joints, skin, eyes and biliary tract, although nearly every organ may be involved. Some of the EIMs are clearly related to intestinal disease activity (i.e. erythema nodosum, peripheral arthritis, orofacial lesions), whereas others occur independently (i.e. pyoderma gangrenosum, anterior uveitis/iritis, ankylosing spondylitis, primary sclerosing cholangitis). Many extraintestinal disorders may be direct inflammatory and metabolic complications of the intestinal inflammation (i.e. osteoporosis, growth retardation, nephrolithiasis, ureteral obstruction, thromboembolic disease).

In this review we provide an overview on the prevalence and clinical aspects of the more commonly reported EIMs of Crohn's disease and ulcerative colitis in pediatric patients, focusing on specific issues of children affected by IBD (growth failure and metabolic osteopathy).

Key Words:

IBD, Extradigestive manifestations IBD, Pediatrics IBD.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are systemic disorders that often involve extradigestive organs. These nonintestinal affections are collectively denominated extraintestinal manifestations and may not always coincide with the underlying bowel disease.

There are only few published data on the occurrence of these manifestations in children and adolescents affected by IBD. The prevalence of EIMs in recent population based studies of patients with IBD ranges from 6% to 47%[1-4]. Several reports indicate a greater prevalence in children. A recent review by Stawarski et al[5] reported that 50% of patients with UC and 80% of those with CD had at least 1 EIMs. The organs most commonly involved are joints, skin, eyes and biliary tract, although nearly every organ may be implicated. The pathogenesis of these manifestations is not well understood, but an immunologically mediated mechanism is suggested. It has been hypothesized that antigen cross-reactivity shared by extraintestinal organs may be responsible for some of the extraintestinal localizations of IBD. A key role of the intestinal microflora for the dysregulatory activation of the intestinal immune system and the induction of the chronic inflammatory process in bowel and extraintestinal organs is suggested by animal models. In HLA-B27 transgenic and T cell receptor-α mutant colitis mouse models, the expression of extraintestinal and intestinal disease involve the presence of commensal bacteria; these mouse models do not experience intestinal or extraintestinal inflammation in germ-free environments[6]. Genetic factors have been implicated in the pathogenesis of EIMs in IBD.

EIM, like IBD, have a familial predisposition with a high concordance rate among twins. An association with genes in the HLA region has been established for some of the immunologically mediated extraintestinal manifestations (i.e. uveitis/irits, primary sclerosing cholangitis, ankylosing spondylitis). For examples, patients with CD who have EIMs are more likely to have HLA-A2, HLA-DR1, and HLA-DQw5, while patients with UC and EIMs

Corresponding Author: Marina Aloi, MD; e-mail: marina.aloi@uniroma1.it

are more likely to have HLA-DR103, B27, and B58 phenotypes[7,8]. Other factors, such as malabsorption, protein-losing enteropathy, intestinal resection, and fistulas can lead to deficiencies of nutrients, proteins, vitamins, and minerals with corresponding clinical consequences. Treatments used in the management of IBD may be associated with many nonintestinal adverse effects.

Extraintestinal manifestations of IBD can be classified in two major groups: the first one includes extradigestive diseases caused by probably immunogenetic mechanisms, and these can be related to intestinal activity disease (i.e. peripheral arthritis, erythema nodosum, apthous ulcer) or independent to intestinal inflammation (i.e. ankylosing spondylitis, pyoderma gangrenosus, primary sclerosing cholangitis, uveitis); the second one includes inflammatory and metabolic complications of IBD (growth failure, osteoporosis and osteopenia, nephrolithiasis) (Table I). Growth failure and metabolic osteopathy are a clinical challenge every day for pediatric gastroenterologist, worsened by the very frequent rate of these complications in children affected by IBD. An impaired linear growth occurs in more than 35% of CD patients. Metabolic osteopathy (osteoporosis/osteopenia) is observed in 41% of pediatric CD patients and 25% of UC patients[9]. In children, IBD may interfere with the attainment and maintenance of peak bone mass, which is the most important determinant of lifelong skeletal health.

Table I. Extraintestinal manifestations and complications of IBD.

Related to intestinal disease activity
Peripheral arthritis
Erythema nodosum
Perianal skin tags
Orofacial lesions
Episcleritis
Cholelithiasis
Independent of intestinal disease activity
Spondylarthropathy
Ankylosing spondylitis
Sacroilitis
Pyoderma gangraenosum
Primary sclerosing cholangitis
Anterior uveitis, iritis
Inflammatory and metabolic complications
Growth failure
Osteoporosis, osteopenia
Nephrolithiasis
Ureteral obstruction and fistulas
Haematologic and thromboembolic complications
Amyloidosis
Pancreatitis

Musculoskeletal Manifestations

Joint manifestations are the most common EIMs in IBD and occur in about 20%-30% of patients[10]. Males and females are equally affected. Symptoms may range from arthralgia to acute arthritis with painful swollen joints. The 2 patterns reported in both children and adults are a peripheral arthritis, and an axial involvement, ankylosing spondylitis or sacroiliitis[11]. There are two types of peripheral arthritis in IBD. Type 1 (pauciarticular) arthritis affects less than five large joints (predominantly of the lower limbs) and the swelling is acute and often self-limiting. Type I arthritis is related to disease activity of the underlying bowel disease. The mean duration is 5 weeks. In a report in children, 5 of 32 patients (16%) with UC and 2 of 9 (22%) with CD had peripheral arthritis[12]. Type 2 (polyarticular) arthritis is a symmetrical polyarthritis, frequently affecting five or more of the small joints (e.g. knuckle joints). Its course is independent of intestinal disease activity and may last for several months[13]. The etiology of peripheral arthritis in IBD is suggested to be a combination of genetic predisposition and exposition to luminal (bacterial) bowel contents. Type 1 IBD arthritis is associated with HLA-DRB1*0103, HLA-B*27 and HLA-B*35, whereas type 2 IBD arthritis is associated with HLA-B*44 and MHC class I chain-like gene A, which is a non classical HLA gene located near the HLA-B on chromosome 6[14,15]. The extension of intestinal inflammation is of particular interest relating the pathogenesis of joint inflammation, as CD patients with colonic involvement are at higher risk of developing arthritis than those with isolated small bowel disease. The axial arthropathies, both spondylitis and isolated sacroiliitis, are rarer than peripheral arthropathy and are reported in 3% to 25% of patients[16,17]. Axial arthropathies are not associated with the activity of underlying inflammatory bowel disease. Ankylosing spondylitis is reported in 5% to 10% of patients with IBD[18]; most are young (adolescents and young adults) and most are HLA-B27 positive. Ankylosing spondylitis affects the vertebral column by progressive ankylosis of the vertebral facet joints and the sacroiliac joints (bamboo spine). Peripheral arthropathy usually responds to treatment of the underlying colitis. Other therapeutic interventions include

rest, physical therapy, and intraarticular steroid injections. For analgetic therapy, nonsteroidal anti-inflammatory drugs and COX-2 inhibitors should be avoided, if possible, due to their potential to activate the underlying IBD[19].

In contrast to peripheral arthropathy, medical or surgical therapy of the underlying IBD does not modify the natural history of the ankylosing spondylitis. Physical therapy is of particular importance to maintain mobility of the spine. Other treatments have included sulfasalazine, mesalamine, methotrexate, and azathioprine. Experience with anti-TNFalpha is limited to adult case series, but improvement of both spondyloarthropathy and active bowel disease has been reported in CD[20,21].

Osteoporosis/Osteopenia

Metabolic osteopathy is increasingly identified as a complication of IBD and its treatment in both children and adults[22,23]. Most, but not all, data suggest that patients with CD are at greater risk than those with ulcerative colitis[24,25]. In a review osteopenia was found in 41% of children with CD and in 25% with UC[5]. In a study of 42 children, Szumera observed bone-mineral disturbances in 57% of cases, with predominance of osteoporosis in children with CD (24%) and osteopenia in those with UC (24%)[26]. In a study about the prevalence of osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment, Walthers reported a rate of osteoporosis of 8% in girls and 20% in boys, similar to adult reports. No-differences were recognized in non-steroid-treated (12%) and steroid-treated (11%) patients[27]. In children, IBD may interfere with the attainment and maintenance of peak bone mass, which is the most important determinant of lifelong skeletal health. Pathogenesis of osteoporosis/osteopenia in IBD is not well understood. Several factors may affect normal bone modelling and remodelling, resulting in decreased bone formation relative to bone resorption[28]. Important potential pathogenetic factors include hypogonadism induced by IBD, malabsorption of calcium and/or vitamin D, low body mass index, corticosteroid exposure, and disease activity with related elevation of inflammatory cytokines[29]. The role of the inflammatory-induced osteopenia has been evaluated and a surface receptor (RANK) localized on osteoclasts that stimulates osteoclastogenesis has been described. Its ligand (RANKL) is induced by proinflammatory cytokines. Osteoprotegerin (OPG) is its decoy receptor and precludes ligation of RANKL to RANK, so preventing bone loss. OPG-RANKL-RANK system has certainly a pivotal role in inflammatory-induced bone loss[30]. Preliminary report about the use of recombinant OPG in inflammation-induced osteoporosis seems to be promising[31].

Bone density can be evaluated using bone densitometry (e.g., dual energy x-ray absorptiometry). The densimetric criteria for bone loss are based on t and z scores, which are standard-deviation scores expressed in relation to reference values in young healthy subjects (t score) or sex- and age-matched healthy controls (z score). Osteopenia is defined as a score of –1 to –2.5, and osteoporosis is a score lower than –2.5. Patients with CD should undergo baseline bone densitometry scans, with follow-up imaging studies recommended at 1 to 2-year intervals for pediatric patients with long-term, high-dose exposure to corticosteroids[32]. Special attention should be directed to ensuring that patients taking corticosteroids have adequate calcium and vitamin D intakes. Bisphosphonates and calcitonin have been used in adults with IBD for the treatment of osteoporosis, but their use in pediatric patients remains to be demonstrated[33].

Mucocutaneous Manifestations

Skin involvement in IBD is relatively common. The incidence varies from 10% to 15% of patients with IBD[34]. Erythema nodosum, pyoderma gangrenosum and oral ulceration are the most common mucocutaneous manifestations in IBD. Erythema nodosum (EN) is the most frequent skin manifestation in IBD, affecting up to 15% of CD adult patients[1,34]. A report based on 41 children with IBD found 4 of 32 (12.5%) children with UC and 5 of 9 (56%) with CD had EN[12]. EN presents as a single or multiple tender red nodules typically on the extensor surface of the lower extremities. Normally it heals without ulceration and the prognosis is good. The etiology of EN is unknown. However, there is a genetic association with a distinct HLA region on chromosome 6 (HLA-B15)[8]. Treatment of the underlying IBD usually results in improving EN lesions and at least 25% of EN will heal spontaneously.

Pyoderma gangrenosum (PG) occurs in 0.5%-2% of patients with IBD and may take a course independent of disease activity[3,17]. Specific prevalence data in children are lacking. PG usually begins as a tender erythematous papule that

spreads rapidly to adjacent skin and develops into a burrowing ulcer with irregular violaceous border, surrounded by an erithematous zone. Lesions are multiple in the majority of patients, and most appear below the knee. PG is found typically on the extensor surfaces of the lower limbs, but may appear in any area of the skin. PG is the most severe skin manifestations in IBD and may develop also before bowel symptoms, during quiescent disease, or even following colectomy. The lesion is painful and often persisting despite adequate therapy. Mild cases usually respond to local and topical therapy, including intralesional corticosteroid, topical cromolyn sodium, and topical 5-aminosalicylic acid. Moderate to severe cases need systemic agents, including oral sulfasalazine, dapsone, corticosteroid, and immunomodulators such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil[35]. Infliximab has shown to be effective in the refractory disease both in children and adults[36-39].

Oral aphtous ulcers occur in 10%-30% of patients with IBD and may appear before the onset of intestinal symptoms of IBD or may parallel intestinal disease. The lesions rapidly resolve once remission is achieved.

Metastatic CD is a granulomatous dermatitis seen in adults, whilst sporadic cases have been described in children[40]. Sweet syndrome (acute febrile neutrophilic dermatosis) is a rare EIMs of IBD and presents as tender, erythematous plaques or nodules affecting the arms, legs, trunk, hands, or faces[41]. Sweet syndrome secondary to azathioprine hypersensitivity has been rarely reported in patients with IBD[42]. Most cases improve with systemic corticosteroids. Metronidazole has been reported to be effective in 1 case[43].

Ocular Manifestations

Ocular involvement occurs in 10% of IBD patients[44]. Patients with CD with colonic involvement are more likely to develop ocular problems than those with small bowel disease alone. Data suggest that asymptomatic transient uveitis is frequent in children with IBD, although progression to severe adult uveal disease is poorly reported[45].

The most common ocular lesions associated with IBD are episcleritis and uveitis. Episcleritis manifests as acute redness, irritation, burning, tender to palpation, without loss of vision. Uveitis can be anterior or posterior. Anterior uveitis is the most common and presents painful eye with visual blurring, and photophobia. Visual acuity is not involved unless the retina or the posterior uveal structures are affected. Diagnosis is made on slit lamp examination, showing flare and cells in the anterior chamber. Ocular manifestation can improve with the treatment of the underlying bowel disease. Prompt treatment of uveitis with topical or systemic steroids is crucial to prevent progression to blindness. Infliximab has shown efficacy in uveitis, in episcleritis, and scleritis[46,47]. Ocular complications also may develop in patients with IBD due to chronic corticosteroid usage. Increased intraocular pressure is reported in 22% of pediatric patients treated with corticosteroids[48]. Nevertheless reports of glaucoma also have been reported in children not exposed to corticosteroids, so indicating an immunological mechanism for its development.

Growth Failure

Nutritional issues and failure to thrive are significant problems afflicting pediatric IBD patients, especially those with CD. Growth failure often is the initial presenting symptom in children with early-onset disease and can pose an ongoing problem during childhood and adolescence[49]. The presence of growth and pubertal delay is a key factor in the management of pediatric IBD. Maintaining adequate nutrition, minimizing inflammation and maximizing treatment off of corticosteroids remains a crucial part of managing the potential growth stunting effects of active IBD, most specifically small bowel CD. A decrease in height velocity below the third centile has been reported in as many as 88% of CD patients before the diagnosis; in half of this group growth failure was documented before the onset of symptoms attributable to CD[50]. During the clinical course of CD, growth failure has been reported in up to 40% of children with CD and in 6-10% of those with UC[51]. Final height below the fifth centile is reported 7-30% of adult patients with a pediatric onset of CD[52].

Growth failure in IBD is secondary to several causal agents. Important pathogenetic factors are malnutrition with decreased intake, increased gastrointestinal losses, malabsorption, psychosocial factors and medication effects. All of these components can certainly impact an individual's nutritional state. Nevertheless, there is increasing evidence that inflammation process *per se* may directly inhibit linear growth and play a major role in the etiology of growth retardation[51].

Growth retardation in IBD is strongly associated with disease activity. Inflammatory mediators such as IL-6 and TNF-alpha play a crucial role in reducing plasmatic levels of IGF-1, the peripheral mediator of the growth hormone[53]. Impressive catch-up growth can be observed as soon as remission of intestinal inflammation is achieved. It is essential that height, weight, puberty staging and bone age are accurately and regurarly measured and recorded in young patients with IBD. Nutritional supplementation and need for "catch-up" growth should be an important part of the evaluation of a pediatric IBD patient. Exclusive enteral feeding with polymeric feeds for 6-8 weeks has the advantage of combining anti-inflammatory properties with an increase in energy intake, and is thus ideal for patients with growth failure[54]. Administration of growth hormone was examined in a pilot study (7 patients) and did not demonstrate any effect on growth[55]. The effectiveness of infliximab in improving linear growth in pediatric CD patients has been reported[56,57].

Hepatobiliary Manifestations

The most common serious hepatobiliary complication among pediatric patients is primary sclerosing cholangitis (PSC), a chronic cholestatic liver disease characterized by inflammation and progressive obliterative fibrosis of the intrahepatic and/or extrahepatic bile ducts[58]. Implementation of endoscopic retrograde cholangiopancreatography in children has led to increased frequency of diagnosis. Data from tertiary referral centers suggest a prevalence of PSC in 1.6% to 7.4% of patients with UC[59,60]. A large study conducted in 1500 adolescent and adult patients reported a prevalence of hepatobiliary disease of 5.5% in patients with extensive colitis and 0.5% in patients with distal colitis[61]. The etiology of PSC is unknown. The biliary injury may be initiated by an immune-mediated destruction of the hepatobiliary tract caused by transient infection, or the absorption of bacterial products in genetically predisposed individuals with colonic disease. Perinuclear antineutrophil cytoplasmic antibody titers are elevated in many patients with PSC and UC[62]. Common symptoms are abdominal pain, fatigue, jaundice, hepatosplenomegaly, fever and weight loss, but it is not rare the isolate finding of abnormalities in liver biochemical markers (first of all alkaline phosphatase). In fact, 30% of pediatric patients are asymptomatic[63]. Liver biopsies show ductular, portal, and peripheral inflammatory infiltrates, bile-duct proliferation, periductal fibrosis, and varying degrees of bridging fibrosis. Therapeutic strategies evaluated in adult patients with PSC include corticosteroids, azathioprine, methotrexate, cyclosporine, pentoxiphylline, tacrolimus, bezafibrate, and antibiotics. To date, none of these treatments has been demonstrate to modify the natural history of disease, including patient survival and need of liver transplantation. In children with PSC, ursodeoxycholic acid demonstrated effectiveness in improving liver biochemical markers, but the course of the disease remains unchanged[64]. Transhepatic or endoscopic balloon dilation and short-term stenting of strictures have provided clinical improvement of symptomatic strictures. Relief of strictures by surgical, endoscopic, or interventional radiological techniques for symptomatic strictures has prolonged survival time. Orthotopic liver transplantation can successfully treat children with PSC, with excellent long-term patient and graft survival[64].

Genitourinary Manifestations

Nephrolithiasis, obstructive uropathy, and fistulization of the urinary tract are directly associated with the underlying bowel disease activity. Reported incidence varies from 4% to 23% in adult patients. In children with IBD the estimated prevalence is only 1% to 2%[3]. Nephrolithiasis is more frequent in CD than in UC[65]. Calcium-oxalate stones are the most common and are caused by hyperoxaluria due to increased oxalate absorption in the presence of unabsorbed fatty acids in the colon. The fatty acids compete with oxalate to bind calcium, displacing the oxalate, which can then be absorbed as unbound sodium oxalate across colonocytes and excreted into the urine. The sudden onset of severe abdominal (or beck or flank) pain in patients with IBD, particularly if different from the usual discomfort, should lead to hypothesize a renal stone in the differential diagnosis.

The management of nephrolithiasis in patients with IBD is similar to that in the general population and consists of analgesia, hydration, and alkalinization of urine for uric-acid stones, lithotripsy, and surgery. Urological manifestations in patients with IBD may include ureteral calculi, enterovesical fistula, perivesical infection, perinephric abscess, and obstructive uropathy with hydronephrosis. Fistulous disease complicating the urinary tract in patients with CD may present with pneumaturia or recurrent uri-

nary tract infections. Glomerulonephritis presenting with proteinuria and hematuria has been reported in children and adults with CD or UC[66]. Diagnosis is by renal biopsy, and treatment is that of the underlying IBD.

A rare complication is renal amyloidosis due to chronic inflammation; it mainly occurs in CD and is rarer in UC. Amyloidosis in patients with IBD often involves the kidney and presents with proteinuria followed by nephritic syndrome and subsequent renal failure or death. The diagnosis is confirmed by detection of amyloid (Congo red staining). Therapy is based on colchicine and renal transplantation[67].

Pancreatic Manifestations

Acute pancreatitis may be associated with both UC and CD. The most common cause is iatrogenic (3% of cases of pancreatitis in IBD patients). Many drugs used in the therapeutic strategy of IBS, such as sulfasalazine, mesalamine, 6-mercaptopurine, and azathioprine, can induce pancreatic injury. Drug-induced pancreatitis typically occurs within the first weeks after starting therapy; the course is mild and usually resolves after discontinuation the drug. Stawarski et al[68] reported acute pancreatitis in 4.5% of children with CD and 5.1% of those with UC. Diagnosis is confirmed by computed tomography with contrast, magnetic resonance imaging, or endoscopic retrograde cholangiopancreatography.

Hematological Manifestations

Anemia is the most common hematological manifestation of IBD. Several mechanisms coexists in the development of the various forms of anemia, including chronic intestinal bleeding, chronic inflammatory disease, inadequate dietary iron intake or absorption, vitamin B12 malabsorption secondary to terminal ileal disease or ileal resection, and folate deficiency due to proximal small-bowel disease or sulfasalazine therapy. Azathioprine and sometimes sulfasalazine and 5-aminosalycilic acid can induce a transitory myelosuppression[69]. In children affected by IBD anemia is reported more frequently in CD (70% of patients) than in UC (5% of patients)[3]. Plasma erythropoietin levels often are low in patients with IBD, in conjugation with severe anemia. Treatment of anemia depends on the underlying causes. Symptomatic anemia requires therapy with iron (oral or intravenous), blood transfusion, whilst replacement of deficient vitamins may be required in other types. Recombinant erythropoietin has been successfully used in some patients with IBD and refractory anemia[69].

Patients with IBD are at increased risk of developing thromboembolic complications. In adults the incidence ranges from 1.2% to 6.1%. Thromboembolism is rarer among children with IBD; Paradis et al have described 3 patients with UC and 1 with CD with thromboembolic complications[70]. Several prothrombotic risk factors, such as immobilization, fluid depletion, inflammation, surgery, steroid therapy, and use of central venous catheters contribute to this increased risk in IBD patients. In active disease the development of thromboses may be related to thrombocytosis and increased concentrations of acute-phase reactants. Inflammatory mediators and hypercoagulation are involved in the pathogenesis of IBD, and some proinflammatory cytokines such as interleukin-6 are thrombogenic[71]. Prevention includes adequate control of disease activity, vitamin supplementation and elimination of removable risk factors.

Pulmonary Manifestations

Various pulmonary manifestations have been reported in IBD including large and small airway dysfunction as well as obstructive and interstitial lung disease. These pulmonary dysfunctions do not typically relate to the severity or activity of the underlying IBD. Sulfasalazine-associated lung disease, although rare, is observed after at least 2 months of therapy and includes eosinophilic pneumonia, fibrosing alveolitis, and interstitial pneumonitis. Other pulmonary disorders that have been associated with IBD include bronchiolitis, bronchiectasis, pulmonary vasculitis, apical fibrosis, and granulomatous lung disease.

Cardiovascular Manifestations

Pericarditis has been described in a few case reports of children and adults with IBD[72,73]. The pathogenesis is unknown, but in some cases side events of therapy (e.g., sulfasalazine and mesalamine) have been involved[74]. The clinical symptoms are chest pain, dyspnea, or in severe cases pericardial tamponade.

Neurological Manifestations

There are some isolated reports of neuropathies in patients with IBD, and include optic neuritis[75], peripheral neuropathies[76], and sensorineural hearing loss[77]. Autoimmune mecha-

nisms are proposed for involvement with IBD. Nutritional deficiencies associated with neurological manifestations, such as vitamin B12 deficiency, can be involved. Drugs for treatment of IBD (e.g. metronidazole) also are associated with neurological defects.

Conclusions

This paper has reviewed the epidemiological and clinical characteristics of extraintestinal manifestations of IBD in childhood. IBD are systemic disorders and commonly present extraintestinal manifestations. Almost every organ can be involved by the inflammatory process.

Data related to incidence, prevalence, and clinical presentation of EIMs in children are lacking. The knowledge of these aspects may be essential to improve our understanding of natural history of pediatric IBD. Growth failure and metabolic osteopathy are important issues in the pediatric age group. Prevention, early diagnosis and adequate therapy of EIMs are essential to increase children's health and quality of life.

References

1) Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001; 96: 1116-1122.

2) Juillerat P, Mottet C, Froehlich F, Felley C, Vader JP, Burnand B, Gonvers JJ, Michetti P. Extraintestinal manifestations of Crohn's disease. Digestion 2005; 71: 31-36.

3) Jose FA, Heyman MB. Extraintestinal manifestations of inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2008; 46: 124-133.

4) Mendoza JL, Lana R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M. Extraintestinal manifestations in inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis. Med Clin 2005; 125: 297-300.

5) Stawarski A, Iwanczak B, Krzesiek E, Iwanczak F. Intestinal complications and extraintestinal manifestations in children with inflammatory bowel disease. Pol Merkur Lekarski 2006; 20: 22-25.

6) Rath HC, Herfarth HH, Ikeda JS, Grenther WB, Hamm TE Jr, Balish E, Taurog JD, Hammer RE, Wilson KH, Sartor RB. Normal luminal bacteria, especially Bacteroides species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. J Clin Invest 1996; 98: 945-953.

7) Roussomoustakaki M, Satsangi J, Welsh K, Louis E, Fanning G, Targan S, Landers C, Jewell DP. Genetic markers may predict disease behavior in patients with ulcerative colitis. Gastroenterology 1997; 112: 1845-1853.

8) Orchard TR, Chua CN, Ahmad T, Cheng H, Welsh KI, Jewell DP. Uveitis and erythema nodosum in inflammatory bowel disease: clinical features and the role of HLA genes. Gastroenterology 2002; 123: 714-718.

9) Boot AM, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut 1998; 42: 188-194.

10) Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005; 129: 827-836.

11) Passo MH, Fitzgerald JF, Brandt KD. Arthritis associated with inflammatory bowel disease in children. Relationship of joint disease to activity and severity of bowel lesion. Dig Dis Sci 1986; 31: 492-497.

12) Grossman BJ, DeBenedetti CD. Extraintestinal manifestations of chronic inflammatory bowel disease in children. Proc Inst Med Chic 1970; 28: 119.

13) Lindgren A, Wallerstedt S, Olsson R. Prevalence of Crohn's disease and simultaneous occurrence of extraintestinal complications and cancer. An epidemiologic study in adults. Scand J Gastroenterol 1996; 31: 74-78.

14) Orchard TR, Thiyagaraja S, Welsh KI, Wordsworth BP, Hill Gaston JS, Jewell DP. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. Gastroenterology 2000; 118: 274-278.

15) Orchard TR, Dhar A, Simmons JD, Vaughan R, Welsh KI, Jewell DP. MHC class I chain-like gene A (MICA) and its associations with inflammatory bowel disease and peripheral arthropathy. Clin Exp Immunol 2001; 126: 437-440.

16) Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol 1996; 23: 29-34.

17) Monsén U, Sorstad J, Hellers G, Johansson C. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. Am J Gastroenterol 1990; 85: 711-716.

18) Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol 2006; 20: 451-471.

19) Cipolla G, Crema F, Sacco S, Moro E, de Ponti F, Frigo G. Nonsteroidal anti-inflammatory drugs and inflammatory bowel disease: current perspectives. Pharmacol Res 2002; 46: 1-6.

20) Kruithof E, De Rycke L, Roth J, Mielants H, Van den Bosch F, De Keyser F, Veys EM, Baeten D. Immunomodulatory effects of etanercept on peripheral joint synovitis in the spondyloarthropathies. Arthritis Rheum 2005; 52: 3898-3909.

21) Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum 2005; 52; 1216-1223.

22) Gokhale R, Favus MJ, Karrison T, Sutton MM, Rich B, Kirschner BS. Bone mineral density assessment in children with inflammatory bowel disease. Gastroenterol 1998; 114: 902-911.

23) Schoon EJ, Blok BM, Geerling BJ, Russel MG, Stockbrügger RW, Brummer RJ. Bone mineral density in patients with recently diagnosed inflammatory bowel disease. Gastroenterology 2000; 119: 1203-1208.

24) Loftus EV Jr, Crowson CS, Sandborn WJ, Tremaine WJ, O'Fallon WM, Melton LJ 3rd. Long-term fracture risk in patients with Crohn's disease: a population-based study in Olmsted County, Minnesota. Gastroenterology 2002; 123: 468-475.

25) Ardizzone S, Bollani S, Bettica P, Bevilacqua M, Molteni P, Bianchi Porro G. Altered bone metabolism in inflammatory bowel disease: there is a difference between Crohn's disease and ulcerative colitis. J Intern Med 2000; 247: 63-70.

26) Szumera M, Landowski P, Kami_ska B, Góra-Gebka M, Popadiuk S, Renke J. Bone mineral density in inflammatory bowel diseases in children. Med Wieku Rozwoj 2006; 10: 445-451.

27) Walther F, Fusch C, Radke M, Beckert S, Findeisen A. Osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment. J Pediatr Gastroenterol Nutr 2006; 43: 42-51.

28) Croucher PI, Vedi S, Motley RJ, Garrahan NJ, Stanton MR, Compston JE. Reduced bone formation in patients with osteoporosis associated with inflammatory bowel disease. Osteoporosis Int 1993; 3: 236-241.

29) Vestergaard P. Prevalence and pathogenesis of osteoporosis in patients with inflammatory bowel disease. Minerva Med 2004; 95: 469-480.

30) Vidal NO, Brändström H, Jonsson KB, Ohlsson C. Osteoprotegerin mRNA is expressed in primary human osteoblast-like cells: down-regulation by glucocorticoids. J Endocrinol 1998; 159: 191-195.

31) Redlich K, Hayer S, Maier A, Dunstan CR, Tohidast-Akrad M, Lang S, Türk B, Pietschmann P, Woloszczuk W, Haralambous S, Kollias G, Steiner G, Smolen JS, Schett G. Tumor necrosis factor alpha-mediated joint destruction is inhibited by targeting osteoclasts with osteoprotegerin. Arthritis Rheum 2002; 46: 785-792.

32) Ross PD. Osteoporosis. Frequency, consequences, and risk factors. Arch Intern Med 1996; 156: 1399-1411.

33) Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348: 1535-1541.

34) Hoffmann RM, Kruis W. Rare extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2004; 10: 140-147.

35) Powell RJ, Holbrook MR, Stevens A. Pyoderma gangrenosum and its treatment. Lancet 1997; 350: 1720-1721.

36) Kugathasan S, Miranda A, Nocton J, Drolet BA, Raasch C, Binion DG. Dermatologic manifestations of Crohn disease in children: response to infliximab. J Pediatr Gastroenterol Nutr 2003; 37: 150-154.

37) Barrie A, Plevy S. Treatment of immune-mediated extraintestinal manifestations of inflammatory bowel disease with infliximab. Gastroenterol Clin North Am 2006; 35: 883-893.

38) Regueiro M, Valentine J, Plevy S, Fleisher MR, Lichtenstein GR. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. Am J Gastroenterol 2003; 98: 1821-1826.

39) Gupta AK, Skinner AR. A review of the use of infliximab to manage cutaneous dermatoses. J Cutan Med Surg 2004; 8: 77-89.

40) Yu JT, Chong LY, Lee KC. Metastatic Crohn's disease in a Chinese girl. Hong Kong Med J 2006; 12: 467-469.

41) Ytting H, Vind I, Bang D, Munkholm P. Sweet's syndrome–an extraintestinal manifestation in inflammatory bowel disease. Digestion 2005; 72: 195-200.

42) El-Azhary RA, Brunner KL, Gibson LE. Sweet syndrome as a manifestation of azathioprine hypersensitivity. 1: Mayo Clin Proc 2008; 83: 1026-1030.

43) Banet DE, McClave SA, Callen JP. Oral metronidazole, an effective treatment for Sweet's syndrome in a patient with associated inflammatory bowel disease. J Rheumatol 1994; 21: 1766-1768.

44) Mintz R, Feller ER, Bahr RL, Shah SA. Ocular manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2004; 10: 135-139.

45) Rychwalski PJ, Cruz OA, Alanis-Lambreton G, Foy TM, Kane RE. Asymptomatic uveitis in young people with inflammatory bowel disease. J AAPOS 1997; 1: 111-114.

46) Diaz-Valle D, Miguelez Sanchez R, Fernandez Espartero MC, Pascual Allen D. Treatment of refractory anterior diffuse scleritis with infl iximab. Arch Soc Esp Oftalmol 2004; 79: 405-408.

47) Fries W, Giofre MR, Catanoso M, Lo Gullo R. Treatment of acute uveitis associated with Crohn's disease and sacroileitis with infliximab. Am J Gastroenterol 2002; 97: 499-500.

48) Tripathi RC, Kirschner BS, Kipp M, Tripathi BJ, Slotwiner D, Borisuth NS, Karrison T, Ernest JT. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. Gastroenterology 1992; 102: 1957-1961.

49) Stephens M, Batres LA, Ng D, Baldassano R. Growth failure in the child with inflammatory bowel disease. Semin Gastrointest Dis 2001;12: 253-262.

50) Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology 1988; 95: 1523-1527.

51) Ballinger AB, Camacho-Hübner C, Croft NM. Growth failure and intestinal inflammation. Q J Med 2001; 94: 121-125.

52) Marx G, Seidman EG, Martin SR, Deslandres C. Outcome of Crohn's disease diagnosed before two years of age. J Pediatr 2002; 140: 470-473.

53) Ballinger AB, Azooz O, El-Haj T, Poole S, Farthing MJG. Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of undernutrition in a rat model of colitis. Gut 2000; 46: 694-700.

54) Fernandez-Banares F, Cabre E, Esteve-Comas M, Gassull MA. How effective is enteral nutrition in inducine clinical remission in active Crohn's disease? A meta-analysis of the randomized clinical trials. J Pediatr Gastroenterology Nutr 1995; 19: 356-364.

55) Calenda KA, Schornagel IL, Sadeghi-Nejad A, Grand RJ. Effect of recombinant growth hormone treatment on children with Crohn's disease and short stature: a pilot study. Inflamm Bowel Dis 2005; 11: 435-441.

56) Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, Liu G, Travers S, Heuschkel R, Markowitz J, Cohen S, Winter H, Veereman-Wauters G, Ferry G, Baldassano R; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007; 132: 863-873

57) Baldassano R, Braegger CP, Escher JC, DeWoody K, Hendricks DF, Keenan GF, Winter HS. Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. Am J Gastroenterol 2003; 98: 833-838.

58) Angulo P, Lindor KD. Primary sclerosing cholangitis. Hepatology 1999; 30: 325-332.

59) Bernstein CN. Extraintestinal manifestations of inflammatory bowel disease. Curr Gastroenterol Rep 2001; 3: 477-483.

60) Rasmussen HH, Fallingborg J, Mortensen PB, Freund L, Tage-Jensen U, Kruse V, Rasmussen SN. Primary sclerosing cholangitis in patients with ulcerative colitis. Scand J Gastroenterol 1992; 27: 732-736.

61) Olsson R, Danielsson A, Järnerot G, Lindström E, Lööf L, Rolny P, Rydén BO, Tysk C, Wallerstedt S. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology 1991; 100: 1319-1323.

62) Duerr RH, Targan SR, Landers CJ, LaRusso NF, Lindsay KL, Wiesner RH, Shanahan F. Neutrophil cytoplasmic antibodies: a link between primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1991; 100: 1385-1391.

63) Feldstein AE, Perrault J, El-Youssif M, Lindor KD, Freese DK, Angulo P. Primary sclerosing cholangitis in children: a long-term follow-up study. Hepatology 2003; 38: 210-217.

64) Lidén H, Norrby J, Gäbel M, Friman S, Olausson M. Outcome after liver transplantation for primary sclerosing cholangitis. Transplant Proc 2001; 33: 2452-2453.

65) Gasche C. Complications of inflammatory bowel disease. Hepatogastroenterol 2000; 47: 49-56.

66) Wilcox GM, Aretz HT, Roy MA, Roche JK. Glomerulonephritis associated with inflammatory bowel disease. Report of a patient with chronic ulcerative colitis, sclerosing cholangitis, and acute glomerulonephritis. Gastroenterology 1990; 98: 786-791.

67) Lovat LB, Madhoo S, Pepys MB, Hawkins PN. Long-term survival in systemic amyloid A amyloidosis complicating Crohn's disease. Gastroenterology 1997; 112: 1362-1365.

68) Stawarski A, Iwanczak F. Incidence of acute pancreatitis in children with inflammatory bowel disease. Pol Merkur Lekarski 2004; 17: 33-36.

69) Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anemia, and inflammatory bowel disease. Gut 2004; 53: 1190-1197.

70) Paradis K, Bernstein ML, Adelson JW. Thrombosis as a complication of inflammatory bowel disease in children: a report of four cases. J Pediatr Gastroenterol Nutr 1985; 4: 659-662.

71) Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340: 448-454.

72) Frid C, Bjarke B, Eriksson M. Myocarditis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1986; 5: 964-965.

73) Patwardhan RV, Heilpern RJ, Brewster AC, Darrah JJ. Pleuropericarditis: an extraintestinal complication of inflammatory bowel disease. Report of three cases and review of literature. Arch Intern Med 1983; 143: 94-96.

74) Agnholt J, Sørensen HT, Rasmussen SN, Gøtzsche CO, Halkier P. Cardiac hypersensitivity to 5-aminosalicylic acid. Lancet 1989; 1: 1135.

75) Sedwick LA, Klingele TG, Burde RM, Behrens MM. Optic neuritis in inflammatory bowel disease. J Clin Neuroophthalmol 1984; 4: 3-6.

76) Nemni R, Fazio R, Corbo M, Sessa M, Comi G, Canal N. Peripheral neuropathy associated with Crohn's disease. Neurology 1987; 37: 1414-1417.

77) Akbayir N, Calis AB, Alkim C, Sökmen HM, Erdem L, Ozbal A, Bölükba_ F, Akbayir N. Sensorineural hearing loss in patients with inflammatory bowel disease: a subclinical extraintestinal manifestation. Dig Dis Sci 2005; 50: 1938-1945.