World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i1.45

World J Gastroenterol 2014 January 7; 20(1): 45-52
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Current issues in pediatric inflammatory bowel disease-associated arthropathies

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Received: September 25, 2013 Revised: October 17, 2013
Accepted: November 3, 2013
Published online: January 7, 2014

Abstract

Joint involvement is the most common extraintestinal manifestation in children with inflammatory bowel disease (IBD) and may involve 16%-33% of patients at diagnosis or during follow-up. It is possible to distinguish asymmetrical, transitory and migrating arthritis (pauciarticular and polyarticular) and spondyloarthropathy (SpA). Clinical manifestations can be variable, and peripheral arthritis often occurs before gastrointestinal symptoms develop. The inflammatory intestinal pattern is variable, ranging from sub-clinical inflammation conditions, classified as indeterminate colitis and nodular lymphoid hyperplasia of the ileum, to Crohn's disease or ulcerative colitis. Unlike the axial form, there is an association between gut inflammation and evolution of recurrent peripheral articular disease that coincides with a flare-up of intestinal disease. This finding seems to confirm a key role of intestinal inflammation in the pathogenesis of SpA. An association between genetic background and human leukocyte antigen-B27 status is less common in pediatric than n adult populations. Seronegative sacroiliitis and SpA are the most frequent forms of arthropathy in children with IBD. In pediatric patients, a correct therapeutic approach relies on the use of nonsteroidal antiinflammatory drugs, local steroid injections, physiotherapy and anti-tumor necrosis factor therapy (infliximab). Early diagnosis of these manifestations reduces the risk of progression and complications, and as well as increasing the efficacy of the therapy.

Key words: Inflammatory bowel disease; Spondyloarthropathy; Sacroiliitis; Infliximab; Extraintestinal manifestations

Core tip: Extraintestinal manifestations in pediatric patients with inflammatory bowel disease (IBD) are very common and are often underestimated, despite provoking a significant impairment of quality of life of patients. This review examines recent literature concerning joint involvement in the course of IBD, focusing on the most important aspects regarding classification of forms of arthropathy, pathogenesis and the essential elements for a correct diagnostic and therapeutic approach.

Cardile S, Romano C. Current issues in pediatric inflammatory bowel disease-associated arthropathies. *World J Gastroenterol* 2014; 20(1): 45-52 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i1/45.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i1.45

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of unknown etiology characterized by involvement of the gastrointestinal tract and association with certain characteristics, such as familial history, intermittent course, good responsiveness to steroids and high prevalence of extraintestinal manifestations

(EIMs)[1]. The most common EIMs affect articulations, cutis, eyes and mouth[2]. The finding of an involvement of different organs and systems leads to the assumption of the presence of predisposing common risk factors. Joint involvement is the most common EIM in children with IBD, which may involve 16%-33% of patients at diagnosis or during follow-up. It is possible to recognize both peripheral and axial forms with a broad clinical spectra, which can be transient and mild to persistent and disabling. In patients with IBD, the diagnosis of arthritis is essentially clinical and radiological; since magnetic resonance imaging (MRI) has become commonly used in clinical practice, it is possible to recognize early forms of articular manifestations[3].

ARTICULAR INVOLVEMENT IN IBD

Articular-peripheral complications and axial involvement occur in 23% and 4%, respectively, of IBD adult patients[4]; in this group, 1 out of 5 shows peripheral arthritis, axial arthritis or both[5,6]. Stawarsky *et al*[7] carried out an epidemiological study on pediatric IBD patients that confirmed IBD-associated arthropathy in 7%-25% of patients. Although in some studies, there was an increased prevalence of arthritis in the pediatric population compared to adults[8], with female prevalence. In a recent retrospective, prospective study, the phenotypic expression of the disease between patients with childhood-onset IBD (133 pediatric patients) and adulthood-onset (179 adult patients) cases was evaluated, observing that EIMs in pediatric age patients were more frequent (14.3% *vs* 7.3%) and joint involvement had the same incidence (4.1% *vs* 4.5%)[9]. Lakatos *et al*[10] have suggested that in 29% of pediatric IBD there was a risk of developing EIMs within a follow-up period of 15 years. Dotson *et al*[11] examined the rates of EIMs in a pediatric IBD population, and reported the prevalence of arthralgias (17%), followed by aphthous stomatitis (8%) and arthritis (4%). Furthermore, joint symptoms were correlated with severity and activity of intestinal disease. Orchard *et al*[12] proposed a classification of enteropathic peripheral arthropathies in adults, distinguishing between Type 1 (pauciarticular, large, inferior articulations) and Type 2 arthritis (polyarticular, small, superior articulations). Type 1 arthritis (4%-17% of patients with Crohn's disease, CD) is correlated with IBD-activity and affects less than five joints (usually ankles, knees, hips, wrists and, sometimes, elbows and shoulders) with evidence of swelling or effusion. Type 2 (2.5% of patients with CD) follows a course independent of the activity of IBD, with persistent symptoms. Type 1 arthritis is more frequent in adult patients with stenosing and penetrating perianal CD, and twice as frequent in patients with colonic and ileocolonic disease, as opposed to patients with ileal disease. Another form of arthritis has been proposed, type 3 peripheral, which includes patients with both axial involvement and peripheral arthritis.

Axial forms are different, with a clinical course generally independent of IBD activity index, and sacroiliitis (SI) may also be asymptomatic in 50% of patients with CD[13,14]. In ulcerative colitis (UC), articular complications are more frequent in patients with pancolitis, as opposed to patients with proctitis or left-sided UC[15].

CLASSIFICATION OF SPONDYLOARTHROPATHIES

Spondyloarthropathies (SpAs) are defined as a group of chronic inflammatory diseases characterized by a pauciarticular spondyloarthropathy, peripheral, or asymmetrical arthritis, with or without axial involvement[16]. SpAs are considered a variety of EIMs of IBD, and the clinical features, which are initially not well defined, evolve over time, becoming clearer at a later stage. The classification proposed by Amor *et al*[17] and Dougados *et al*[18] includes clinical entities such as axial forms; SI; ankylosing spondylitis (AS); reactive arthritis (ReA), which usually occurs because of infective enteritis, especially Salmonella, Shigella, Yersinia or Campylobacter; peripheral arthritis, usually asymmetrical, affecting main articulations; psoriatic arthritis; seronegative enthesopathy and arthropathy syndrome and enthesitis; uveitis and IBD-associated arthropathy (Table 1). To group all forms of arthritis that begin before the age of 16 years, experts in pediatric rheumatology, the International League of Associations for Rheumatology[19], have developed a classification of juvenile idiopathic arthritis (JIA), revised in 2004, which includes seven subgroups: (1) systemic arthritis; (2) oligoarthritis; (3) polyarthritis (rheumatoid factor negative); (4) polyarthritis (rheumatoid factor positive); (5) enthesitis related arthritis; (6) psoriatic arthritis; and (7) undifferentiated arthritis (originally called "other arthritis"). In this classification, in contrast to the European Spondyloarthropathy Study Group (ESSG) criteria, there is the exclusion of children with a family history of psoriasis, and the absence of ReA and IBD as forms of SpA. IBD appears only as a descriptor of enthesitis related arthritis forms, but the term is not defined, even if UC and CD can clearly be associated with human leukocyte antigen (HLA)-B27, undifferentiated SpA, or even AS[20,21].

The most commonly accepted classification criteria for SpAs, used in clinical practice, come from the ESSG (Table 1). These criteria are superior to the earlier New York modified criteria for the diagnosis of AS (Table 1), but are inadequate in describing the full clinical peculiarities of SpAs, as they exclude some manifestations[22] (Table 1). Furthermore, this classification has not proved very useful in defining patients with forms of early arthritis (*e.g.*, less than 1 year of onset); in fact, it was drawn up before MRI became commonly used in clinical practice. To overcome these defects, in particular to enable diagnosis before the appearance of radiological damage, other classifications have been validated. The most recent is the Assessment of SpondyloArthritis International Society criteria for the classification of axial[23,24] and peripheral spondyloarthritis[25]. They are an innova-

Table 1 Classification of spondyloarthropathies

Spondyloarthropathies: Five major subtypes
Ankylosing spondylitis (AS)
Reactive arthritis (ReA)
Psoriatic arthritis
Enteropathic arthritis or arthritis associated with inflammatory bowel disease
Undifferentiated spondyloarthropathy
European spondyloarthropathy study group
Classification criteria for spondyloarthropathy
Inflammatory spinal pain OR synovitis (asymmetrical or predominantly in the lower limbs) plus any one or more of the following:
Positive family history
Alternate buttock pain
Psoriasis
Enthesopathy
Inflammatory bowel disease
Sacroiliitis
Modified New York criteria for the diagnosis of ankylosing spondylitis
Unilateral sacroiliitis grade 3 or 4, or bilateral sacroiliitis grade 2 to 4 together with at least one of the following:
Low back pain of at least three months' duration improved by exercise and not relieved by rest
Limited motion of lumbar spine in sagittal and frontal planes
Decreased chest expansion relative to normal values for age and sex
Musculoskeletal manifestations of spondylarthropathies
Peripheral arthritis: one or more swollen and tender joint (s); synovitis is asymmetric and predominantly in lower limbs
Inflammatory spinal pain: symptoms of back pain in lumbar, dorsal or cervical regions associated with at least four of the following: (Calin's criteria)
Onset before age 45 yr
Insidious onset
Improved by exercise
Associated with morning stiffness
Duration of at least three months
Dactylitis: evidence of "sausage digit" on examination
Peripheral enthesitis: achilles tendinitis and/or plantar fasciitis
Buttock pain
Anterior chest wall pain

tion compared to the previous criteria (ESSG and Amor *et al*[17]), but still have limitations in clinical practice, especially if applied in a pediatric population[26]. Although Amor's and the ESSG criteria were derived from a population of adult patients with SpA, they might be applied specifically in juvenile onset SpA.

PATHOGENESIS

Factors that determine the presence of SI and AS remain unclear; however, HLA-27 typing may be a potential factor. The frequency of HLA B27 in the IBD population is generally not higher compared with the general population. HLA-B27 confers an additional risk for inflammatory low back pain in patients with IBD[27]. A prospective study concerning genetic variability in these populations has found a significantly higher rate of HLA B27 in patients with IBD and AS compared with those with undifferentiated SI. HLA B27 can detect 60%-90% of patients with SI diagnosed at a young age who subsequently develop AS[28]. Another candidate gene, CARD 15, is described in association with CD[29], but studies have not demonstrated any association with extra-intestinal involvement. De Vos *et al*[30] found a striking association between a CARD 15 polymorphism and SI (78% in patients with SI *vs* 48% without SI). No studies have been carried out on the association of CARD 15 and SpA in children with CD. In conclusion, seronegative SI and SpA are the most frequent forms of arthropathy in children with IBD, especially in CD. In these patients, it may be useful to carry out a screening with Rx of the lombo-sacral rachis, also in the absence of typical symptoms. A transmembrane glycoprotein, E-cadherin, has been identified in the literature. It mediates the intercellular adhesion of epithelial cells, which, for its role of receptor for CD103, is considered a marker of monocyte-derived inflammatory dendritic cells that may contribute to the pathogenesis of chronic T cell-mediated colitis[31]. Demetter *et al*[32] showed that expression of E-cadherin is high in the gut of patients with IBD and in patients with SpA[33]. Moreover, this integrin was found in subclinical acute and chronic gut inflammation, as an early event in the development of this process. Other alterations common in the two groups concern $CD4^+$ T cells (Th1 cells, Th2 cells, Th17 cells and regulatory T cells). Initial studies have shown Th1 predominance in the intestinal mucosa of patients with IBD and SpA. Recent studies have suggested that, in both groups of patients, Th17 cells may have an important role in the initiation and perpetuation of autoimmune inflammation[34]. Many studies have established an important role of toll-like receptors (TLRs) in the innate immune response against pathogenic microorganisms. Several studies have shown increased expression of TLR-4 and TLR-2 in APCs of patients with SpA.

Immunopathological overlap between gut inflamma-

tion and SpA has been demonstrated. Intestinal inflammation is believed to play a key role in the pathogenesis of SpA[35]. It has been hypothesized in some studies that ileocecal inflammation may be considered an important risk factor in the occurrence of SI. Ileocolonscopies performed in adults with AS, without clinical intestinal symptoms, have shown inflammatory infiltrate of the ileum mucosa in 65% of subjects examined compared with 3% in a control group[36]. Studies carried out on patients with SpA have exhibited ileal and colonic inflammatory infiltrate in the lamina propria, with signs of architectural distortions[37]. Mielants *et al*[38], in another study on adult patients with AS, demonstrated an inflammatory gut histological pattern with "acute" inflammatory infiltrations, characterized by a well preserved architecture with neutrophil- and eosinophil-like epithelial infiltrate, with no significant lymphocyte infiltrate. This "chronic" pattern, with histological alterations similar to those in IBD (crypt distortion and/or atrophy, cryptitis, and/or crypt with increased rate of mixed cells and lymphoid aggregates in the lamina propria), was classified as indeterminate colitis (IC)[39] and was less frequent. Subclinical intestinal lesions are most frequent in a pediatric population (75% of cases) with undifferentiated SpA (peripheral arthritis); in 16% of cases (2/12), CD occurred during follow-up[40].

Conti *et al*[41], in 129 children with SpA and clinical symptoms suggestive for IBD, used ileocolonscopy to confirm a diagnosis of IBD only in seven (5%), while 12 (9%) had IC, and in 12 (9%) patients, intestinal nodular lymphatic hyperplasia was present as a main characteristic. Subclinical intestinal inflammation in patients with SpA is frequent in pediatric populations, and a long-term follow-up may be needed to determine if IC and intestinal nodular lymphatic hyperplasia can be considered as early forms of IBD.

DIAGNOSTIC APPROACH

In patients with IBD, the diagnosis of arthritis, both peripheral and axial, is essentially clinical and radiological, as there is no reliable laboratory test that can be used as a diagnostic tool for diagnosis and management of these arthropathies[42].

Early diagnosis of inflammatory arthritis in IBD patients may prevent disability caused by SpA and AS[43]. Lakatos *et al*[44] reported SI as the most frequent arthropathy in CD (20%) compared to UC (15%) and predominantly in females, especially in children. SI is clinically characterized by lower back pain and involves the lumbosacral region with functionally impaired rachis. The gold standard for diagnosis is a radiography (Rx) of the lumbosacral rachis following the radiological criteria expressed in the modified New York classification[45,46]. Orchard *et al*[47] compared MRI with the gold standard in adult patients, adapting the New York criteria to MRI of the rachis: the results obtained with the latter imaging technique were much more accurate and specific. Their study, carried out on a population of patients with CD, revealed that about 39% of patients showed signs of SI detected by MRI, while previous studies showed signs of SI in 20% of IBD patients diagnosed with Rx[48].

SpAs associated with IBD are placed in differential diagnosis with other pathologies with osteo-articular involvement, including osteoarthritis, rheumatoid arthritis and arthritis associated with connective tissue diseases, such as lupus, arthralgia (which may complicate corticosteroid withdrawal), osteonecrosis related to corticosteroids, and infliximab (IFX) related lupus-like syndrome.

However, in many cases, intestinal involvement is underestimated in patients with SpA, because these patients often have no intestinal symptoms and high levels of blood markers of inflammation are erroneously attributed only to the joint disease. For this reason, in clinical practice, it may be necessary to use noninvasive investigations on the gut for a preliminary assessment of patients with suspected intestinal disease. Serum levels of human cartilage glycoprotein 39 (also called YKL-40) were recently found to be higher than normal in IBD patients with arthropathies, suggesting that this protein could be used as a disease activity marker in arthritis associated with IBD. Moreover, we can use certain leukocyte proteins, such as lactoferrin and calprotectin, as markers of the presence of leukocytes in stools, to assess intestinal inflammation. Serological tests focus on several antibodies, such as perinuclear anti-neutrophil cytoplasmic antibodies and anti-Saccharomyces cerevisiae antibodies, used in combination to increase sensitivity. Additional serum biomarkers include antibodies against outer membrane porin C, the pseudomonas fluorescens bacterial sequence I2, bacterial flagellin and the anti-glycan antibodies, *i.e.*, anti-chitobioside IgA, anti-laminaribioside IgG and antimannobioside[49].

Other non-invasive methods of screening patients presenting arthropathies where intestinal involvement is suspected, include abdominal ultrasound to visualize bowel wall thickness and capsule endoscopy of the small intestine to detect intestinal inflammation before performing endoscopic evaluation[50].

THERAPY

Treatment of arthritis and arthropathy associated with IBD is based almost entirely on extrapolation from therapy for other forms of arthritis. The therapeutic approach in IBD-associated arthropathies must be oriented towards treatment of the prevalent disease (articular *vs* intestinal disease) with the identification the best approach. Conventional treatment depends on clinical presentation (axial disease, peripheral arthritis, enthesopathy) or associated features (uveitis, psoriasis, colitis). Lee *et al*[51] have proposed a therapeutic algorithm for patients with SpA indicating specific anti-inflammatory molecules, such as nonsteroidal anti inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2), for axial and peripheral arthropathies, in a 1st level treatment, while

Table 2 European Crohn's and colitis organization recommendations

Peripheral arthritis: Short term treatment with non-steroidal anti-inflammatory agents, local steroid injections and physiotherapy (primary focus for underlying Crohn's disease)
Persistent peripheral arthritis: Sulfasalazine
Axial arthropathy: Intensive physiotherapy associated with non steroidal anti inflammatory drugs
Ankylosing spondylitis and Crohn's disease intolerant or refractory to non steroidal anti inflammatory drugs: Anti-tumour necrosis factor therapy

sulphasalazine, mesalazine or methotrexate (MTX) were recommended in moderate peripheral arthritis, in addition to intra-articular steroid injections and physiotherapy. NSAIDs may worsen an existing colitis[52], although it has also been observed that therapies with COX2 inhibitors, which last up to 2 wk, have not induced any relapses in patients with UC[53]. In IBD-associated arthropathies, MTX, azathioprine or Sulphasalazine are considered to be ineffective or marginally effective if axial symptoms predominate, as opposed to peripheral arthritis[54-56]. The two main biological agents targeting tumor necrosis factor (TNF)-α are the chimeric monoclonal IgG1 antibody (IFX), and the 75 kD IgG1 fusion protein (Etanercept)[57]. Several trials have confirmed the effectiveness of IFX, especially in AS[58,59]. IFX and etanercept are also effective in the treatment of rheumatic symptoms, such as peripheral arthritis and SI in IBD patients[60]. Few data are available regarding the efficacy of etanercept in pediatric patients with IBD-associated arthritis[61]. Sandborn *et al*[62] confirmed the inefficacy of Etanercept on control of intestinal disease in patients with SI or AS, and IBD. It was demonstrated that Etanercept, despite controlling the musculoskeletal features associated with arthritis, and in particular entheseal, is not effective in controlling colitis in patients with Crohn's SpA, suggesting that the effect of TNF-α blockade in SpA differs between the joint and the bowel[63]. On the other hand, IFX has proven effective in inducing and maintaining endoscopic and clinical remission in pediatric CD[64]. Brandt *et al*[65] reported beneficial effects of IFX on axial and peripheral symptoms in patients with CD and Kaufman *et al*[66] confirmed the efficacy of IFX in EIMs of CD. Ellman *et al*[67] described four patients with CD arthritis where IFX has induced clinical improvement with reduced need for corticosteroids. Generini *et al*[68] have proposed a therapeutic flowchart in SpA associated with CD, with the use of IFX at a dose of 5 mg/kg. A maintenance schedule provided infusions every 5-8 wk, and results showed clinical remission in both intestinal and articular diseases for 12-18 mo. IFX appears to be the drug of choice for treating both pathologies.

Braun *et al*[69], in a multicenter randomized trial, demonstrated the persistent clinical efficacy and safety of anti-TNF therapy with IFX (5 mg/kg) in patients with AS over 5 years of almost continuous treatment, with low rates of drug-related adverse events.

Current ECCO recommendations suggest the use of short-term treatment with NSAIDs, local steroid injections and physiotherapy in CD patients with arthropathies with better control of the intestinal disease. In the case of axial arthropathy, NSAIDs are considered first-line drugs, but in the case of refractory or intolerant forms to NSAIDs, anti-TNF agents are recommended[70] (Table 2).

Adalimumab (ADA) is effective at inducing and maintaining remission in children with CD, and is effective for UC patients with loss of response or with adverse effects secondary to IFX[71,72]. ADA has also been studied in pediatric patients with rheumatic diseases, with demonstrated efficacy in pediatric patients with JIA[73] and ERA[74]. However, data relating to ADA use in pediatric patients with joints disease associated with IBD are scarce.

CONCLUSION

IBD, which includes CD and UC, can be a painful and debilitating condition. In addition to bowel symptoms, patients with IBD often experience extraintestinal complications, such as arthritis, kidney and liver disease, eye disorders and skin problems. Of these, arthritis is the most common - occurring in about 25% of all pediatric IBD sufferers. Evidence indicates that a dysregulation of mucosal immunity in the gut of IBD causes an overproduction of inflammatory cytokines into the bowel, thus leading to an uncontrolled intestinal inflammation with joints involvement. TLR variants and abnormalities, altered function and balance of T-cell subpopulations and their production of proinflammatory cytokines, as well as integrin and E-cadherin dysfunction, are partially responsible for the pathogenesis of these complex diseases. Medical treatment of rheumatic manifestations of IBD includes sulfasalazine and mesalamine, immunomodulators and TNF-α inhibitors. As our understanding of the pathophysiology of ERA, enthesitis, and sacroiliitis improves, and with the advent of additional biological therapies, the prognosis of children and adolescents with arthropathies associated with IBD will likely improve.

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ISSN 1007-9327
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