Association of juvenile idiopathic arhrtitis and functional constipation

The authors present case reports with juvenile idiopathic arthritis being associated with functional constipation but not with inflammatory bowel disease. The cause of megacolon was only cleared in one case in the form of Hirschprung's disease. The skeletal symptoms could be classified as seronegative spondylathropathy. Surgical treatment resulted in the remission of arthritis in one case and a possible pathogenic explanation is discussed. Common genetic predisposition is a plausible explanation, but fecal stasis leading to increased permeability to macromolecules, increased exposure to microbial and dietary antigens, loss of tolerance to own bacterial flora and host susceptibility to the increased antigenic load may stand in the background of this infrequent and not yet described association between juvenile idiopathic arthritis and functional constipation.

KEYWORDS: bacterial colonization ■ constipation ■ Hirschprung's disease ■ JIA ■ juvenile idiopathic arthritis

Anna Bazso[1,3†], Krisztina Sevcic[3], Ilonka Orban[3], Gabor Suto[2], Gyula Poor[3], Emese Kiss[1] & Zsolt Balogh[3]

[†]Author for correspondence:
[1]Clinical Immunology and Rheumatology Department, National Rheumatology and Physiotherapy Institute, Frankel Leo str. 38-40, Budapest H-1023, Budapest, Hungary
Tel.: +36 1438 8300
Fax: +36 1438 8337
bazsoanna@yahoo.com
[2]University of Pécs, Pécs, Hungary
[3]National Rheumatology and Physiotherapy Institute, Budapest, Hungary

Inflammatory bowel disease (IBD) can often be associate with spondylarthropathies (SpA). It is well known that reactive arthritis can appear after bacterial gastrointestinal infections such as *Salmonella*, *Shigella*, *Yersinia*, *Brucella* and *Escherichia coli*. IBDs, such as ulcerative colitis (UC) and Crohn's disease (CD), are sometimes accompanied with oligoarthritis, predominantly affecting lower limb joints. Following these infections, not only reactive arthritis and SpA, but also juvenile idiopathic arthritis (JIA) can appear. Besides IBD and enteric infections, appendicitis may also contribute to the development of arthritis [1]. Ileocolonoscopic studies have demonstrated the role of the gut in different forms of arthritis and histological gut lesions; however, both demonstrate different aspects and can be subdivided into two forms: the acute inflammatory type, such as in bacterial enteritis, and the chronical type, which can also be divided into two main categories – IBD (UC and CD) and nonclassified colitis such as indeterminate colitis (IC) after colectomia, and unclassified IBD (IBDU; lack of the symptoms of CD or CU criteria) [2].

There are few publications on the association of JIA and megacolon [3,4]. The most frequent background/cause of the megacolon is Hirschprung disease (megacolon congenitum), which is characterized by the absence of the Meissner's and Auerbach's vegetative plexi in the distal part of the colon. The lack of peristalsis results in a continuous spasm and partial obstructions of the involved segment, with enlargement of the properly innervated colon due to intestinal stasis. In addition to genetic factors [5], there are data to support the role of other toxic agents in the background of this disease (granulomatosus enterocolitis, amoebiasis or pseudomembranosus colitis and collagenosus colitis) [2,6–9].

We present four cases of association between arthritis and megacolon. Each of the patients belonged to the goup of SpA. The histories of arthritides were similar in all of the four cases. Hirschprung's disease was verified in only one case. The etiology of the other three cases remained obscured. Gut histology was not specific for either UC or CD. However, although the exact patomechanism is unknown, the association of the two diseases support the fact that there is a strong connection between impaired colonic motor activity and locomotor inflammation.

This case report presents four patients to demonstrate this rare association. These cases are reported to focus our attention to this interesting problem. However, a systematic review of the 1000 cases followed up at our department has not been performed yet.

Patient code: M.M, male, 2 February 1989

The patient's chronic obstipation was observed from a very early newborn age. A Recamieren larging was carried out in 1997, but thereafter, abdominal cramp, distension and encopresis developed again. In 2003, Type 1 diabetes

future medicine part of fsg

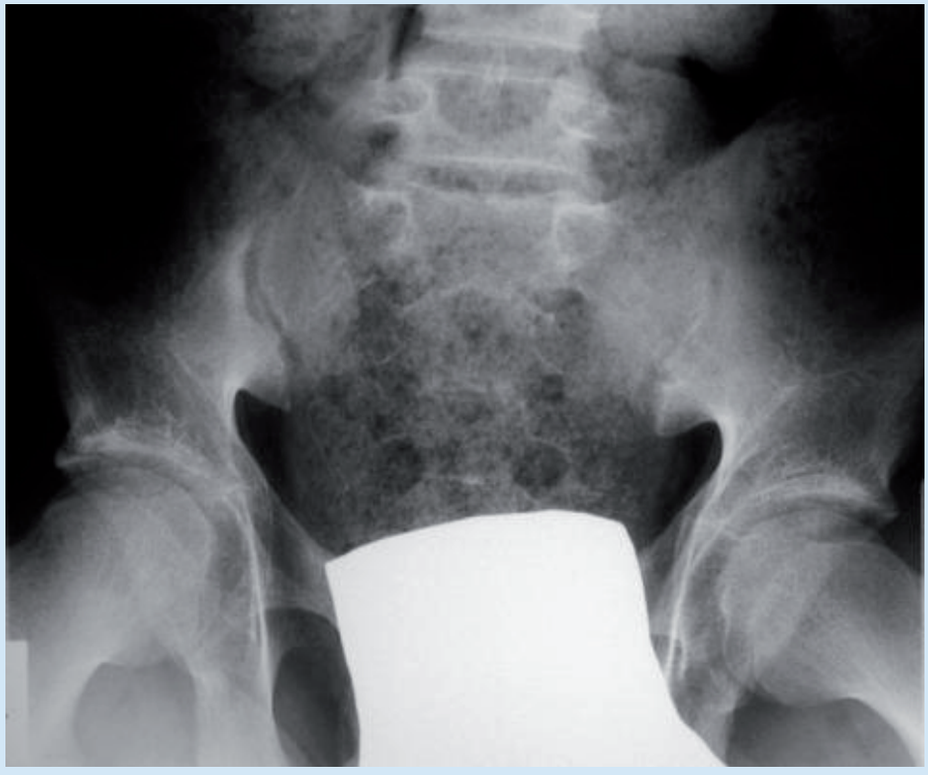

Figure 1. Patient code: ZS. D. The sacroiliac space is tightened and there is partial ankylosis in the left side.

mellitus was verified. The history and elevated chloride level referred to cystic fibrosis. When the patient was 16 years old, articular complaints began with pain in the right hip, then in the left ankles and knees became painful and swollen with inability to walk. The laboratory results showed inflammation, C-reactive protein (CRP) levels of 190 mg/l and the erythrocyte sedimentation rate (ESR) at 80 mm/h. At the presentation, an anorectic boy of low height was seen with a distended, tender abdomen and scibalas in the left iliac fossa. ESR was elevated and the CRP level was 148 mg/l. The abdominal ultrasonography detected meterorism. The sacral x-ray was unable to analyze the sarcoiliac status because the colon was filled with feces. The patient presented as HLA B27 positive. The rapid onset of oligoarthritis of the lower extremities with fever suggested the reactive arthritis group; sulfasalazin therapy was started. In 2007, the patient presented with fever and diarrea, and painless defence caused an abdominal emergency. Because of an extremely enlarged colon, total colectomy with ileostoma was performed. Histology showed necrosis of colonic mucosa but this was not related to UC; atypical antineutrophil cytoplasm antibody and anti-*Saccharomyces cerevisiae* mannan antibodies were negative. Hirshprung's disease was excluded, since histology showed a significant amount of ganglions. After the operation, the patient became complaint and symptom free, also with regard to the arthritis.

Patient code: ZS.D, male, 9 September 1994

Abdominal defence was presented soon after the patient's birth but spontaneous defecation was not detected. The clinical signs suggested the presence of Hirschprung's disease. Transversostomy was placed at 2 months of age and the rectal biopsy did not show any submucosal or intramural plexus. When the patient was 2 years of age, Swenson intervention was performed and the tightened part of the colon was removed. Arthritis began at the age of 12 years, with his right knee becoming swollen and painful, and the ESR was 50 mm/h. With regard to the Hirschprung's disease, reactive arthritis was the most possible diagnosis but the laboratory tests showed ESR to be 56 mm/h, white blood cells were 7.2 g/l, CRP levels were 7 mg/l, rheumatoid factor and antinuclear antibody were negative but HLA-B27 was positive, and the pelvis x-ray demonstrated that the left sacroiliac surface had been narrow.

An oligoarticular form of JIA with HLA-B27 positivity was diagnosed, and the patient was treated with methotrexate, salazopyrin, hydroxochloroquine, aurothiomalate, cyclosporin and leflunomide. Arthritis is still active with bilateral sacroileitis and enthesitis. Altough there was no clear link between JIA and Hirschprung's disease, the potential alteration of the gut microflora owing to the previous surgical interventions may connect the two diseases (FIGURE 1).

Patient code: T.H, male, 28 March 1974

The patient presented encopresis from his birth. Abdominal ultrasound demonstrated meteoristic colon; the rectum was filled with feces. Barium enema verified an enormously dilated rectal ampulla without any signs of mechanic obstruction. Rectoscopy revealed inflammatory colonic mucosa, and histopathology was indicative for the chronic asepcific colitis. Arthritis started at age 11 years after a bicycle accident causing injury to the right knee. Arthrocentesis yielded a yellow synovia with a normal cell count without red blood cells. Culture was negative. ESR was higher than normal at 80 mm/h. Reactive arthritis was diagnosed, but antibiotic and plaster therapy were only mildly effective.

The patient was referred to our department for the first time in 1987. This time, bilateral gonarthritis was the presenting symptom and right knee synovectomy was performed. Plantar fascitis of both feet with walking inability started in 1989. Sacroiliac x-ray demonstrated right-side

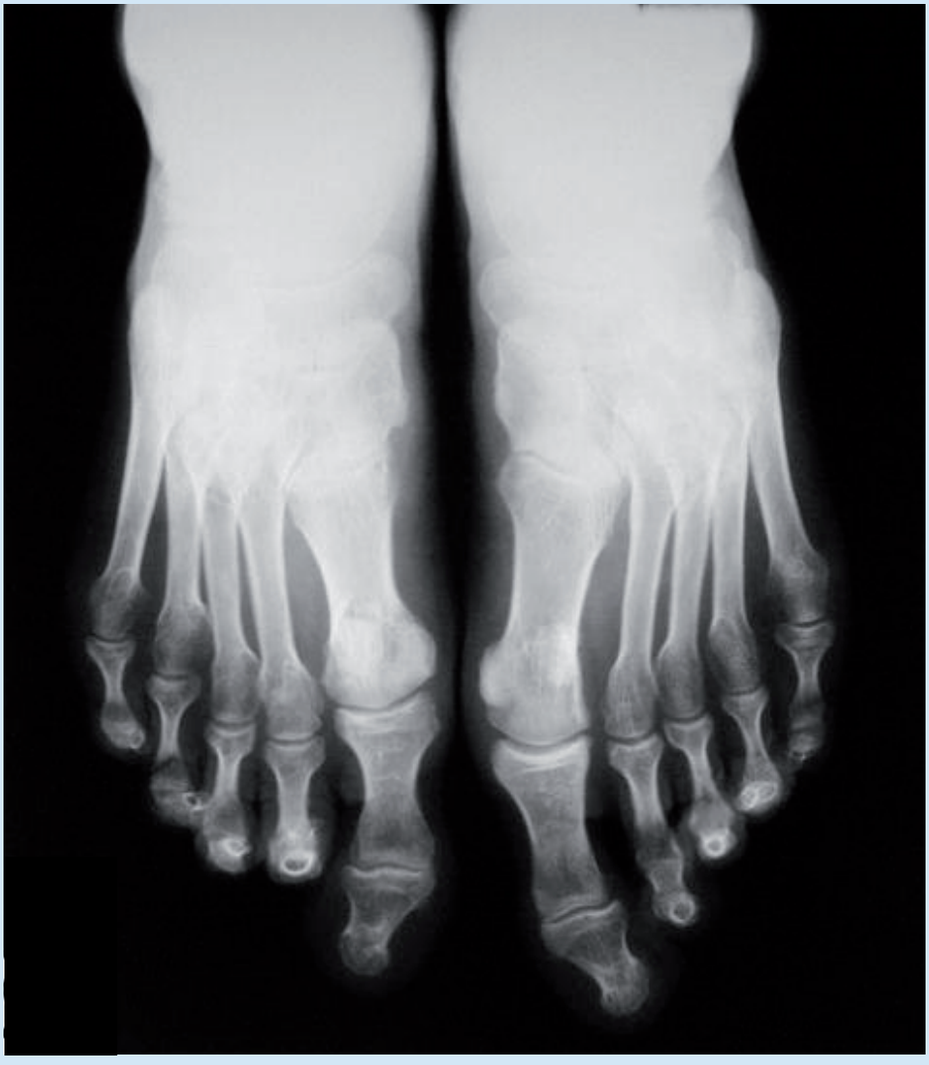

Figure 2. Patient code: T.H. The metatarsophalangeal joint spaces are tightened and the metatarsi are deformed.

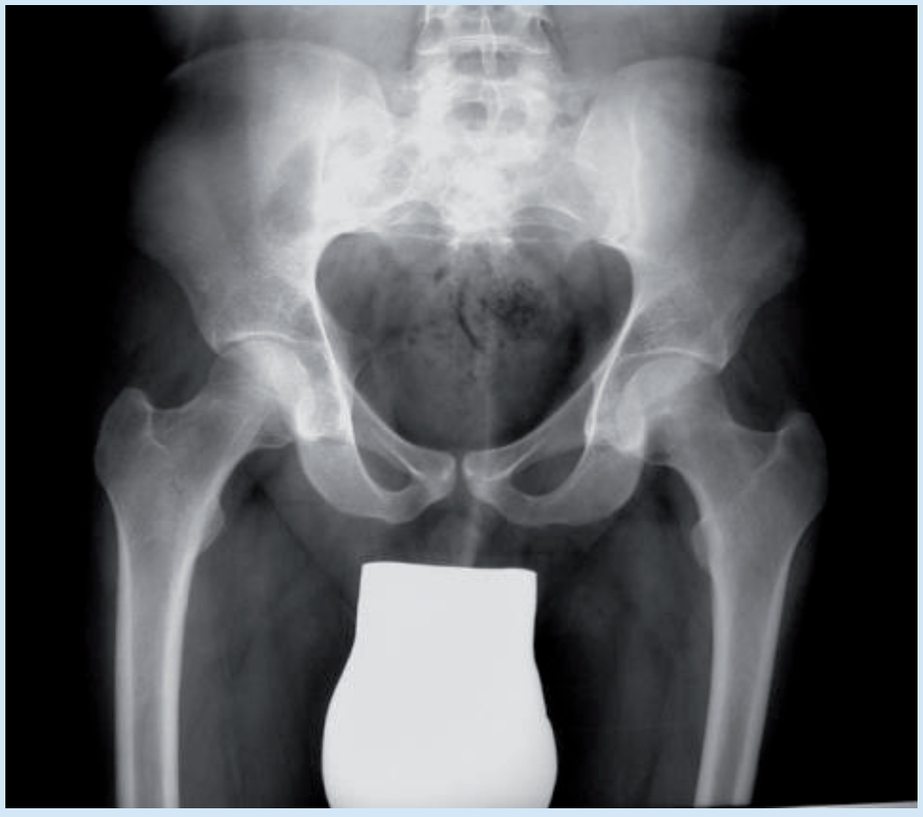

Figure 3. Patient code: Gy.L; moderate juxta-articular osteoporosis. The metatarsophalangeal joint spaces are tightened and there is some erosion in the heads of the metatarsi.

sacroileitis. Laboratory tests presented elevated CRP levels (256 mg/l) and ESR (120 mm/h). The arthritis of the lower extremities seemed to be attributed to SpA. Indomethacine treatment was effective and the patient was complaint free up to 1992. At that time, chronic synovitis of the hands (distal interphalangeal and proximal interphalangeal) and Achilles enthesitis started. This time, the signs of sacroileitis were observed, with persistently elevated inflammatory signs (ESR: 130–78–20 mm/h; CRP: 42 mg/l). In 1996, the patient was hospitalized owing to limited movement of the left hip and lumbar spine and the ESR was 26 mm/h. Clinical and radiological signs of sacroileitis, and HLA-B27 positivity, reinforced the diagnosis of SpA. Methotrexate (7.5 mg/week) therapy was started. Since the patient had fecal incontinence, a barium enema was performed that detected that the colon and rectum were larger than usual. Radiological findings were typical for megacolon congenitum, but further tests to clarify the etiology were not performed. Defecation is facilitated with purgative enemas so no surgical therapy was initiated yet. This time, the patient is arthritis free, but bilateral sacroileitis is justified by x-rays with chronic obstipation (Figure 2).

Patient code: GY.L, male, 7 November 1989

An 11-year-old patient with right ankle pain, swelling and high fever was referred to us. Arthrocentesis excluded septic origin, ESR was 75 mm/h, white blood cells were 8.2 g/l, CRP levels were 9 mg/l, rheumatoid factor was negative and immunserology demonstrated that *Yersinia*, *Brucella*, *Salmonella* and *Borrelia* were also negative. The sacrum, hand and feet x-ray showed no remarkable alterations. The patient suffered from constipation and encopresis from his childhood. The rectum biopsy and histology confirmed hypoganglionosis, and therefore, the Morbus Hirschsprung. Hirschprung's disease was ruled out. Administration of enemas was successful and there was no need for surgical treatment. In 2005, right ankle swelling, pain, fever and walking inability appeared with an ESR of 75 mm/h and CRP levels of 10.3 mg/l. The ultrasound examination detected remarkable/significant

synovitis in his ankle, and sterile synovia was analyzed after arthrocentesis. The genetical analysis resulted negative HLA-B27. During the physical examination, a meteoristic abdomen was palpable with many scibalas in the descending colon. The strong association between reactive arthritis and intestinal disease was supported by the repeated purgative enema that resulted not only in the colonic disease, but also in arthritis relapsus. The further x-ray examinations suggested sacroileitis, since his disease met the criteria system of the classification of JIA. The total colectomy has not yet been carried out because the repeated purgative enema provisionally normalized his abdominal status. The patient has intermittent arthritis episodes at this time because of the untreated/unsolved abnormal abdominal status (FIGURES 3 & 4).

Discussion

A close relationship between different types of intestinal inflammation and SpA is suggested. The association between musculoskeletal involvement and gut pathology is not clearly established.

Pathogens causing gastrointestinal infections or the loss of tolerance against microbiota resident in the intestinal flora are generally accepted to be involved in the development of IBD and associated musculoskeletal symptoms [10]. Joint symptoms develop within 2–3 weeks after the onset of diarrhea in reactive arthritis. Knee, ankle, wrist and sacroiliac joints are usually involved. The most common pathogens are the *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* species with an incidence ranging from 2 to 33%. The risk of developing arthritis is particularly increased following *Yersinia* infection with the presence of the HLA-B27 genotype [11–13]. A high percentage of patients with SpA (90% of patients with ankylosis spondylitis and 70% of patients with undifferentiated SpA) are HLA-B27 positive. However, this marker is not diagnostic for SpA because a significant percentage of the general population is also positive. The disease can further progress into chronic SpA.

There are many cases in which specific bacterial origin of the SpA cannot be confirmed. The human body is associated with microbiota living on external and internal body surfaces. Different mechanisms developed in this ecosystem to maintain appropriate communication between the host and its microbiota to survive [14]. In normal individuals, luminal antigenic exposure results in tolerance rather than immunity. Patients with

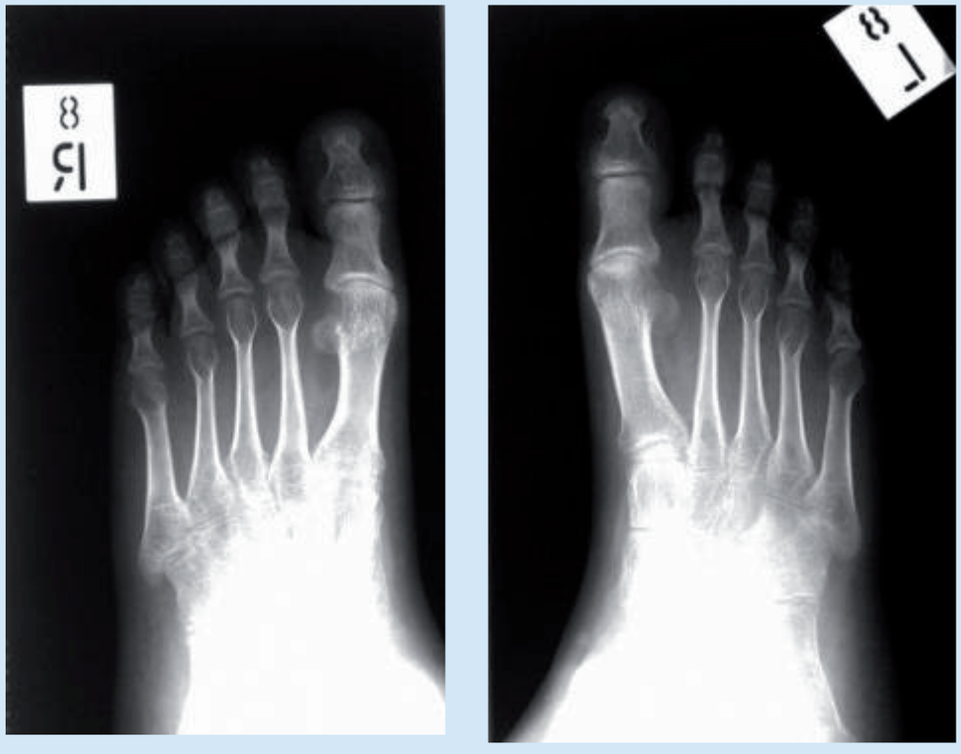

Figure 4. Patient code: Gy.L; tight sacroiliacal joint spaces on both sides with the dominance on the left side. The pelvis is fulfilled by feces and gases.

Box 1. Definitions.

Juvenile idiopathic arthritis

- Juvenile idiopathic arthritis (JIA) is the most common form of persistent arthritis in children before age 16 years. JIA may be transient and self-limited or chronic.

Spondylarthropathy & reactive arthritis

- Spondylarthropathy and reactive arthritis develop in childhood as part of JIA and knee, ankle, wrist and sacroiliac joints are usually involved. There are two subtypes of the diseases: acute and chronic.

Hirschprung's disease

- Hirschprung's disease is caused by the lack of Meissners and Auerbachs vegetative plexi, which results in a partial or total obstruction of the colon.

Inflammatory bowel disease

- Inflammatory bowel disease is characterized by the breach of gastrointestinal wall integrity – increased permeability to macromolecules, increased exposure to microbial and dietary antigens, loss of tolerance to own bacterial flora and increased host susceptibility to increased antigenic load.

Megacolon

- Megacolon is a severe condition characterized by slow colonic transit and impaired defecation resulting in fecal retention and stasis.

Relationship of spondylopathy & inflammatory bowel disease

- Although the association between musculoskeletal involvement and gut pathology is not clearly established, a close relationship between different types of intestinal inflammation and spondylarthropathies is suggested.
- The most common pathogens are the *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* species. The risk of developing arthritis is particularly increased with the presence of the HLA-B27 genotype.

Relationship between musculoskeletal symptoms & megacolon

- Fecal stasis causes increased intestinal permeability for macromolecules, and specific enterogenic bacterial strains may overgrow with accumulation of toxic compounds within the gastrointestinal lumen.

Outcome & treatments

- The fecal stasis and the musculoskeletal inflammation could be treated by sulfasalazin and colectomy.

active IBD lose tolerance to their own bacterial flora, and this loss of tolerance seems to be the cause of IBD. Active IBD is characterized by the following features: a breach of gastrointestinal wall integrity [1], increased permeability to macromolecules [15], increased exposure to microbial and dietary antigens [6], loss of tolerance to own bacterial flora [7], and host susceptibility to the increased antigenic load [8].

Subclinical gut inflammation has also been described in up to two-thirds of patients with SpA; histologic gut inflammation was found in SpA in 30–60% of cases [16]. Examination of histological samples taken during colonoscopy revealed that in acute lesions there is infiltration of the epithelium with neutrophils and eosinophils without a significant increase in lymphocyte count; small superficial ulcers covered with fibrin can be seen and neutrophils overlying hyperplastic lymphoid follicles can occur. The lamina propria is oedematosous and hemorrhagic and contains many polymophonuclear cells. The principal features of chronic lesions are crypt distortion, with atrophy of the villous surface, villous blunting and fusion, increased mixed lamina propria cellularity and basal lymphoid aggregates in the propria. The remission of the arthritis was always connected to the disappearance of the gut inflammation [14,16–18]. Articular remission rates were independent of initial gut inflammation and associated with endoscopic and histologic remission. In addition, initial chronic gut inflammation implies a high risk of evolution of ankylosis spondylitis [4,5].

A recent study presented four cases where megacolon was associated with reactive arthritis or seronegative SpA. Megacolon is a severe condition characterized by slow colonic transit and impaired defecation resulting in fecal retention and stasis [19]. This pathology may result in locomotor inflammation by several mechanisms. The human gastrointestinal tract is not a complete barrier, it is permeable to some macromolecules. Fecal stasis causes impaired mucosal blood flow [20], increases intestinal permeability for macromolecules and specific enterogenic bacterial strains may overgrow with accumulation of toxic compounds within the gastrointestinal lumen [21]. Antigens and toxic agents may freely enter through the disturbed colonic barrier, exposing gut-associated lymphoid tissue to an excess load. The main clue for the role of fecal stasis in the development of arthritis is that musculoskeletal inflammation was resolved

after colectomy in one patient of our four cases. Furthermore, the treatment of gastrointestinal disease usually improves extra-intestinal symptoms as well. Sulphasalazin, which has an anti-inflammatory effect in both IBD and peripheral arthritis, is considered to normalize gut permeability, preventing the entrance of antigens through the defective gut wall [22]. Although the mechanism of this improvement is not fully understood, this observation suggests that these two clinical entities share common pathologic processes [2]. Furthermore, arthritis/sacroileitis can theoretically affect the normal defecation and colonic transit, resulting in secondary obstipation. There are scarce data regarding defecation or obstipation in SpA, but the manipulation of the spine during kyphosis correction resulted in abdominal compartment syndrome in two patients [23]. The effect of arthritis and sacroileitis on gastrointestinal motility needs further investigation.

In conclusion, these four cases with severely impaired colonic motility have demonstrated that fecal stasis and gut inflammation play a crucial role in the pathogenesis of SpA [6].

Future perspective

The association between muskuloskeletal disorders and the gastrointestinal tract has been well known for a long time. Recent developments in the fields of genetic and immunobiological research opened wide perspectives for studying connections between gastrointestinal diseases and muskuloskeletal symptoms (**Box 1**).

Cases of the combination of childhood arthritis and functional colonic disorders require attention for patholgy that is not only associated with specific IBD suptypes (CD and colitis ulcerosa). Other types of gastrointestinal alterations may be connected to arthritis as well. These observations may alter the diagnostic and therpaeutic approaches to musculoskeletal disorders.

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Executive summary

- Juvenile idiopathic arthritis (JIA) associated with inflammatory bowel disease is common, but with functional constipation is extremely rare.
- Megacolon is a severe condition characterized by slow colonic transit and impaired defecation resulting in fecal retention and stasis.
- The cause of megacolon could be Hirschprung's disease and the skeletal symptoms could be classified as seronegative spondylathropathy.
- Hirschprung's disease is caused by the lack of Meissners and Auerbach vegetative plexi, which results in partial or total obstruction of the colon.
- The human gastrointestinal tract is not a complete barrier, it is permeable to some macromolecules and antigens and toxic agents may freely enter through the disturbed colonic barrier.
- Arthritis/sacroileitis can theoretically affect normal defecation and colonic transit, resulting in secondary obstipation.
- Sulfasalazin and surgical treatment could result in remission of arthritis and obstipation as well.

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