

Histopathological features of gastrointestinal mucosal biopsies in children with juvenile idiopathic arthritis.

Abstract

Objective: The association between inflammatory bowel disease and joint involvement is well established but there is a paucity of data describing histopathological features of the gut in relation to juvenile idiopathic arthritis (JIA).

Methods: We retrospectively identified 34 (22 male) children aged from 3-16 years with JIA (12 oligoarthritis, 5 polyarthritis, 8 systemic onset arthritis, 8 enthesitis-related arthritis and 1 psoriatic arthritis) with significant gastrointestinal symptoms who underwent upper and/or lower endoscopy between 2002-2009. The histopathological findings at the time of endoscopy were reviewed in addition to gastrointestinal symptoms, presence of autoantibodies and concomitant treatment.

Results: In these 34 children the most common gastrointestinal indications for endoscopy were persistent abdominal pain 15/34 (44%) and diarrhoea 11/34 (32%). 29/34 (85%) had gut mucosal inflammation, mostly affecting the colon (80%). Active inflammation of the gut was found in 6/29 (21%) children with one child presenting with features typical of inflammatory bowel disease, 15/29 (52%) showed mild non-specific inflammation. Eight patients (27%) had predominantly an eosinophilic inflammation. Twenty-six of 34 had previously received treatment for JIA. There was a negative association with the use of immunomodulators and the presence of eosinophil inflammation.

Conclusion: The majority of children with JIA and gastrointestinal symptoms have histological evidence of mild non-specific inflammation, but some having active colitis and prominent eosinophil infiltrate.

What is Known about this topic

- Arthritis occurs in 7-25% of children with IBD and may precede the onset of gastrointestinal symptoms.
- Given the association between gut and joint inflammation, little is known about the features of gut inflammation in these children with juvenile idiopathic arthritis.

What This Study Adds:

- There are histological abnormalities in children with JIA with gastrointestinal symptoms.
- The predominant pathological findings were a varying severity of mucosal inflammation ranging from chronic inflammation to active chronic inflammation. In addition eosinophils were a prominent component.

ABBREVIATIONS

CD- Crohn's disease, UC- ulcerative colitis, IBD- inflammatory bowel disease, EIM- extraintestinal manifestation, HPF- high power field, RA- rheumatoid arthritis, JIA- juvenile idiopathic arthritis, RF- rheumatoid factor, Th- T helper type, ANA- anti-nuclear antibodies, EGID- eosinophilic gastrointestinal disorders

INTRODUCTION

Crohn's disease (CD) or ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD) are chronic idiopathic conditions of the gastrointestinal tract with nearly one quarter of cases having onset during childhood or adolescent years [1]. Several studies in adult populations have described increased co-morbidity with other immune-mediated diseases including asthma, arthritis, rheumatoid arthritis (RA), ankylosing spondylitis and psoriasis [1-6]. A paediatric study described a particularly strong association of IBD with RA and systemic lupus in children compared with previous adult studies [1].

Arthritis is a common extraintestinal manifestation (EIM) of several conditions including IBD, bacterial or parasitic infections of the gut, coeliac disease and pseudomembranous colitis. Arthritis is the most frequent EIM, occurring in 7-25% of children with IBD that may precede the onset of gastrointestinal symptoms by years [7,8]. It appears to be more prevalent in patients with large bowel than small bowel disease and in those with complications such as abscesses, pseudomembranous polyposis, perianal disease, massive haemorrhage, erythema nodosum, stomatitis, uveitis, and pyoderma gangrenosum [9].

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and is an important cause of short and long-term disability. It is a clinical diagnosis made in a child less than 16 years of age with arthritis (defined as swelling or limitation of motion of the joint accompanied by heat, pain, or tenderness) for at least 6 weeks' duration with other identifiable causes of arthritis excluded, the physical findings may be associated with raised inflammatory markers and positive findings on radiology. Studies in developed countries have reported a prevalence that

varies between 16 and 150 per 100000 [10]. The International League of Association for Rheumatology classification of JIA includes seven subtypes:

Systemic onset JIA, oligoarticular JIA, polyarticular rheumatoid factor (RF)-positive and RF-negative JIA, Enthesis-related JIA, psoriatic JIA and others or unclassified [11].

Several clues for the close linkage between gut and joint inflammation have been suggested. Alterations in key molecules that regulate the immune response in the gut of patients with enthesitis-related JIA arthritis are similar to those with CD [12]. Changes commonly found in both groups are a high expression of E-cadherin in the gut or toll- like receptors, a T helper type1 (Th1) predominance in the intestinal mucosa, increased proportion of Th17 cells or dysfunction of regulatory T cells [12]. The alteration in function and regulation of these molecules may have an important role in initiation of these diseases. Additionally, increased intestinal permeability has been reported in patients with spondyloarthropathy and IBD, which may alter the local immune response to bacterial antigens or abnormal responses to certain microorganisms [12].

Given the well-known association between gut and joint inflammation, surprisingly little is known about the features of gut inflammation in this group of children with severe joint disease. Mielants et al [13] described 12 patients less than sixteen years of age with late-onset juvenile chronic arthritis who had undergone colonoscopy with biopsies of the colonic mucosa and terminal ileum and gut inflammation was demonstrated in nine (75%). Kokkonen et al [14] examined the prevalence of immune activation in gastrointestinal mucosa in children with JIA or connective tissue disease and found that the majority of children suffering from JIA or CTD with GI symptoms show abnormalities consistent with activation of the intestinal immune system such as

UC or lymphoid nodular hyperplasia, as well in the duodenal bulb, terminal ileum and colon with specific CD 3 lymphocytes in the intestine. Arvonen et al [15,16] could demonstrate that intestinal gamma/delta- intraepithelial lymphocytes are increased in children with JIA and suggested that lymphocyte cytotoxicity is abnormally increased in the intestinal mucosa in JIA.

The aim of this study is to evaluate gastrointestinal mucosal histopathological features in a series of children with juvenile idiopathic arthritis who underwent endoscopic evaluation for significant gastrointestinal symptoms.

METHODS

Patients referred to a paediatric gastroenterology centre during the period January 2002 to December 2009 who underwent gastrointestinal endoscopy for gastrointestinal symptoms with JIA were retrieved from hospital databases. All cases of JIA who had endoscopic examination were identified and medical records were analysed retrospectively. The diagnosis for JIA was made by experienced paediatric Rheumatologists and classified using International League of Association for Rheumatology criteria [17].

Children with JIA with significant bowel symptoms were referred for further evaluation usually by either upper and/or lower endoscopy. Significant gastrointestinal symptoms included diarrhoea, constipation, vomiting, abdominal pain, weight loss, oral aphthous ulcers or per-rectal bleeding.

Demographic data at the time of endoscopy were sex, age at start of JIA and age when endoscopy was performed. In addition to basic demographics, specific types of JIA, types of treatment patients were on at the time of endoscopy; presence of autoantibodies (anti-nuclear antibodies (ANA) and rheumatoid factor (RF)) and HLA-B27 association were reviewed.

All children who underwent endoscopy had routine mucosal biopsies taken from oesophagus, stomach, duodenum, terminal ileum and colon (caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum) following the departmental protocol. Routine formalin fixation, paraffin embedding and sectioning of 4 µm thick sections was performed followed by haematoxylin and eosin staining.

All biopsy specimens were reviewed by a panel, including a consultant Paediatric Pathologist, a clinical scientist with a PhD in paediatric GI pathology, a scientist

whose research area is GI mucosal disease and a consultant academic paediatric gastroenterologist with an interest in inflammatory disease.

Histological features were recorded and compared to the clinical information. For the purposes of this paper there were 4 categories of GI biopsy finding: (1) normal, (2) mild non-specific inflammation, (3) mild inflammation with prominent eosinophils (4) active inflammation. Eosinophilic oesophagitis was defined by the presence of more than 15 eosinophils per HPF [18]. In the colon, although no consensus exists, we considered 30 eosinophils per HPF in the caecum and 20 eosinophils per HPF in the left colon as normal values [19, 20].

To compare endoscopy results especially the incidence of eosinophilia a control group was used. It included 35 children (19 or 54% male, mean age 7.9 ± 3.6 years (range: 2.8 to 15 years) with intractable constipation (defined as per ESPGHAN guidelines [21] as chronic constipation not responding to optimum medical therapy for at least 3 months) have undergone endoscopy.

The baseline characteristics of all patients were evaluated by means of simple descriptive analysis. Continuous variables were presented as median, minimum and maximum values and categorical data as absolute frequencies and proportions. As univariate analyses X^2 test or Fisher exact test were used to compare the different types of JIA or inflammation and location of inflammation. Spearman's rho test was used when appropriate. Statistical analyses were performed using SPSS (version 20.0 Mac; SPSS, Chicago, IL). All statistical tests were 2 tailed using 0.05 level of significance. The study was approved by the local ethical committee as a retrospective review / audit.

RESULTS

Study cohort

We identified 34 children (22 or 65% male) with a diagnosis of JIA who had undergone endoscopy for gastrointestinal symptoms. The median age of onset of JIA was 6.4 years (range: 1.5 to 15.8 years). The median age at time of endoscopy was of 9.2 years (range 3.3 to 16.3 years). The type of JIA was oligoarticular JIA in 12 (35%) cases, polyarticular JIA in 5 (15%) cases, systemic onset JIA in 8 (24%) cases and, enthesitis-related arthritis in 8 (24%) cases JIA and psoriatic JIA in one (2%) child (**Table 1**).

The most common gastrointestinal indications for endoscopy were persistent abdominal pain 15/34 (44%), diarrhoea 11/34 (32%), faltering growth or weight loss 6/34 (17%), per-rectal bleeding 5/34 (15%) and other less common gastrointestinal symptoms were mouth ulcers, haematemesis or constipation. (**Figure 1**). There was no association between the clinical gastrointestinal symptoms and type of JIA using univariate analyses.

In 27 (80%) children an upper and lower endoscopy was performed. In 3 (9%) children an upper endoscopy only and in 4 (12%) children only a lower endoscopy was performed. Histological examination of gut mucosal biopsies demonstrated some gut inflammation in 29/34 (85%) with 5/34 (15%) having normal histology (**Table 2**). There were significant more children with gut inflammation in JIA group compared to the control group with 8/35 (22%) children, $p < 0.001$.

In the upper endoscopy the inflammation was mostly located in the duodenum in 11/29 (38%), stomach in 8/29 (27%), and in 3/29 (10%) both stomach and duodenum was affected.

In the lower endoscopy inflammation was mostly located in the colon in 25/29 (80%) of cases; no child had isolated inflammation in the terminal ileum. In 3/29 (9%) cases both colon and ileum was affected.

In our cohort of patients with abnormal histological features, the majority of children with 11/29 (38%) had involvement of the colon only, 4/29 (14%) had involvement of duodenum and colon, 4/29 (14%) of stomach, duodenum and colon (2 of those included inflammation of the terminal ileum), 2/29 (7%) of stomach and colon and one case of involvement of oesophagus and colon.

Active inflammation was present in 6/29 (21%) children. One child had a new diagnosis of CD at the time of endoscopy where the joint disease was the primary presentation. 15/29 (52%) intestinal mucosal biopsies showed non-specific inflammation and 9 of the 29 patients (27%) had mild inflammatory changes with predominant eosinophils (**Figure 1**). In 5 cases this involved only the colon, in two cases involved TI and colon, and in two cases involved the duodenum and colon.

In the control group 8/35 (22%) had eosinophilic infiltrate not significant to the JIA patients, in all cases exclusively in the colon.

There was no direct correlation between the types of JIA, gut inflammation, type of gut inflammation, clinical symptoms and treatment using X^2 test.

In 28/34 serum autoantibody levels were available. Of the 11/28 (39%) patients with abnormal gut histology, anti-nuclear antibodies were positive in 7/28 (25%) of the patients and rheumatoid factor were positive in 4/28 (14%) cases (2 cases systemic JIA, one case with polyarticular JIA and one case with enthesitis-related arthritis). No

gut-specific autoantibodies had been performed. We did not observe any direct correlation between autoantibodies positivity and types of gut inflammation using univariate analyses.

26/34 received treatment for JIA. One (3%) child of the 29 patients with abnormal histology was on steroids only, 4/29 (13%) patients were on steroids and immunomodulators namely azathioprine and methotrexate, 2/29 (7%) patients were on non steroidal anti-inflammatory drugs (NSAID) and immunomodulators, 7/29 (24%) were on immunomodulators only, and one (3%) child was on tumor necrosis factor inhibitor (etanercept) at the time of the endoscopy. In addition, there were 4 (13%) children on NSAID and 2 (7%) on sulfasalazine (**Table 1 and 2**). Overall 8 (27%) of the 29 children with abnormal histology were not on treatment at the time of endoscopy.

Amongst the group of 5 patients with normal histology, one (20%) child was off treatment, two (40%) were on steroids and immunomodulators, one (20%) on immunomodulators only and 2 (40%) were on sulfasalazine.

When immunomodulators were used no abnormal eosinophilic infiltrate was identified compared to 7 children with no treatment that had eosinophilic infiltration ($p=0.01$). No other association of the immunosuppressive therapy with chronicity of the inflammation or the type of inflammation could be found using univariate analyses.

DISCUSSION

The findings of this study have described the histological abnormalities seen in routine gastrointestinal mucosal biopsies in children with JIA juvenile idiopathic arthritis with significant gastrointestinal symptoms. The predominant pathological findings were a varying severity of mucosal inflammation ranging from mild non-specific inflammation to chronic inflammation. In addition eosinophils were a prominent component.

More than 80% of our cohort of children had abnormal mucosal gut inflammation despite almost half of them having been on immunomodulators at the time of endoscopy. The majority showed colonic inflammation, a finding similar to the previous observation of arthritis as an extraintestinal manifestation occurring more commonly in CD patients with large bowel involvement [22,23].

There was no correlation between gut inflammation and sub-type of JIA. There were more boys than girls in this group of patients despite JIA being commoner in girls [24]. This can be explained by the larger number of systemic-onset JIA with 24% (where the sex incidence is equal) and also 24% enthesitis related arthritis patients (where boys are more often affected than girls). ~~Most cohorts of JIA patients would have around 10% systemic onset patients and around 10-15% enthesitis related arthritis patients. This cohort had 24% systemic onset and 24% enthesitis related arthritis patients.~~ This could have been due to small numbers and so by chance, or GI symptoms may be commoner in these JIA sub-types.

Another speculation about over-representation of systemic onset or enthesitis related arthritis could be that in most of the cases, intestinal symptoms precede or coexist

with joint manifestations, but in some patients, arthritis precedes the gut manifestations, even by several years [12]. This could be investigated further by prospectively collecting data on GI symptoms in a large cohort of JIA patients. Why there were a high number of ERA patients with gut involvement remains unclear. Enthesitis and dactylitis in IBD patients have been studied less well than peripheral arthritis [25]. The prevalence of enthesitis in patients with IBD varies from 5 to 10%, is predominantly seen in Crohn's disease [26].

Prior studies have established altered microbiota and immunologic reactivity to enteric commensal organisms in IBD. Stoll et al. found in children with enthesitis-related JIA a reduced abundance of faecalibacterium in the stool [27]. Differences in the humoral responses to these bacteria may contribute to disease. So ERA patients may also have altered microbiota and immune responsiveness to enteric organisms which could influence gut inflammation [27], however, we do not have any data about microbiota to support this.

Acute inflammation occurred in 6 of 29 patients with abnormal histology. Nine out of 15 patients with mild non-specific inflammation had been on immunomodulators that might have modified their disease activity hence presenting with a much less severe picture. Prevalence of active IBD ~~inflammatory bowel disease~~ could potentially have been even higher.

It was previously noted that in adults with ankylosing spondylitis, 5-10% have inflammatory bowel disease [23]. Approximately 30%-60% patients with spondyloarthropathies have occult intestinal inflammation, which may be related to their ingestion of non-steroidal anti-inflammatory drugs or associated with their rheumatic disease [22]. In a prospective study of 123 patients with

spondyloarthropathies who initially underwent endoscopy, intestinal evolution was evaluated by ileocolonoscopy and an evolution to IBD was recorded in 7% of these patients [28]. Despite the high frequency of gut lesions in patients with joint diseases, only a few patients are symptomatic. In a series described by Cuvelier et al [29], only 27% of patients with histological gut inflammation had intestinal symptoms. In our cohort of JIA children who had undergone endoscopy, all have had significant gastrointestinal symptoms with only a minority having normal histological findings, though there was no correlation with sub-type of JIA. This study cannot comment on the prevalence of subclinical gut inflammation in JIA patients who have no gastrointestinal symptoms.

In nearly 30% eosinophilic gut mucosal inflammation was present in our cohort of children with JIA and in our control group with 22%. Kokkonen et al [14] found that intraepithelial CD3+, α/β +, and γ/δ + lymphocytes counts were increased in children with JIA compared to a control group. The aetiology of this reaction remains unknown, but similar features are seen in delayed-type food allergy. In line with this, Arvonen found that the number of Granzyme B expressing intraepithelial lymphocytes was increased in duodenal mucosa in patients with JIA, hence lymphocyte cytotoxicity is abnormally increased in the intestinal mucosa in JIA. Similar pattern of activation has been seen in food allergy and celiac disease [15,16]. Not also food allergy, but also allergy to medications such as NSRAI might be an explanation. Arvonen et al [15,16] speculated that some luminal, possibly a nutritional factor may be involved in JIA as well. In 22% of our children of the control group with intractable constipation showed eosinophilic infiltrate. In what way our high eosinophilic infiltrate in the gut mucosa could play a role with the previous findings

remains still unclear. But it could be speculated that a direct or indirect activation from intraepithelial lymphocyte might be an explanation but further studies are needed to see whether cytotoxic activation plays any role in the pathogenesis of JIA. A high percentage of nearly 30% eosinophilic gut mucosal inflammation was present in our cohort. There were only 2 previous case reports describing association of eosinophilic gut disease with rheumatoid arthritis in adults [30,31]. The mechanism for the eosinophilic gastrointestinal disorders (EGID) in JIA remains to be established as well the definition of eosinophilic infiltrate in the gut mucosa. A histological finding of eosinophil infiltration (6 cells - high power field (HPF)) in the lamina propria was thought to be a useful threshold for diagnosis of food protein-induced proctocolitis [32,33]. However, DeBrosse et al. recently described that eosinophils (mean 16-20 cells- HPF) were normally observed in the gastrointestinal tract of control children, especially in the colon [34]. Functional studies of EGID are lacking and much needed to understand the physiology and pathophysiological roles of eosinophils in the gastrointestinal tract [35].

~~Management of EGID is comprehensive and may involve routine endoscopies, with biopsies, dietary modifications, and long-term oral medications. It is not uncommon for patients to be put on an elimination diet in an attempt to remove suspected pathogenic foods from the diet. In severe cases, amino acid-based elemental formulas may serve as the sole source of nutrition [24]. Anti-inflammatory steroid drugs have been widely used to treat EGID [25]. Steroid dependent or steroid refractory patients may be treated with thiopurines (azathioprine or 6-mercaptopurine) [25]. Other management strategies include anti-allergic drugs such as mast cell stabiliser disodium cromoglycate and leukotriene antagonist montelukast. Ketotifen and H1-~~

~~antihistamines have been shown to reduce tissue eosinophilia and its symptoms in patients with EG [26].~~ Treating these children with JIA with simple dietary manipulation, in severe cases amino acid-based elemental formulas, anti-histamines and/or thiopurines (azathioprine or 6-mercaptopurine) may be helpful in the management of their gastrointestinal symptoms [36-38]. In our children there was a negative association with the use of immunomodulators and the presence of eosinophilic infiltrate in the intestinal mucosa. Therefore in these patients an earlier start of treatment with immunomodulators might be reasonable.

There are some limitations in this retrospective study. Firstly, this is a highly selected group of children with JIA seen at a tertiary who have gastrointestinal symptoms. This does not represent the whole spectrum of disease in children with JIA. Secondly, there was no direct (blood test) or indirect (faecal calprotectin) evaluation of mucosal inflammation.

In conclusion, our study has described gut mucosal inflammation in children with JIA who presented with gastrointestinal symptoms in a tertiary centre. Hereby we could confirm previous findings and continued to suggest that endoscopy with mucosal biopsies should remain an important investigation for these children. In addition, we could find a high percentage of eosinophilic infiltrate in the intestinal mucosa. The aetiology of this reaction remains unknown, with several possible explanations such as in delayed-type food allergy, allergy to medications such as NSRAI or a pathologic infiltration of intraepithelial lymphocytes. In what way the high eosinophilic infiltrate in the gut mucosa could play a role with the previous findings remains still unclear. Further studies are needed to see whether cytotoxic activation plays any role in the

pathogenesis of JIA and to understand the physiology and pathophysiological roles of eosinophils in the gastrointestinal tract.

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CONFLICT OF INTEREST:

The authors have no conflicts of interest to disclose. There were no financial or personal relationships with other people or organisations that could have inappropriately influenced this work. There were no financial or personal relationships with any company or organisation sponsoring the research at the time the research was done. There was no funding. NJS is part supported by GOSHCC and NIHR GOSH BRC.

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References

1. Kappelman MD, Galanko JA, Porter CQ, et al. Association of paediatric inflammatory bowel disease with other immune-mediated diseases. *Arch Dis Child*. 2011;96:1042-6.
2. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology*. 2005;129:827-6.
3. Cohen R, Robinson D Jr, Paramore C, et al. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002. *Inflamm Bowel Dis*. 2008;14:738-3.
4. Weng X, Liu L, Barcellos LF, et al. Clustering of inflammatory bowel disease with immune mediated diseases among members of a northern california-managed care organization. *Am J Gastroenterol*. 2007;102:1429-5.
5. Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. *Gastroenterology*. 2005;129:819-6.
6. Bardella MT, Elli L, De Matteis S, et al. Autoimmune disorders in patients affected by celiac sprue and inflammatory bowel disease. *Ann Med*. 2009;41:139-3
7. Jose FA, Garnett EA, Vittinghoff E, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15:63-8.
8. Diefenbach KA, Breuer CK. Pediatric inflammatory bowel disease. *World J Gastroenterol*. 2006;12:3204-2.
9. Wordsworth P. Arthritis and inflammatory bowel disease. *Curr Rheumatol Rep* 2000;2:87-8.

10. Weiss JE, Ilowite NT. Juvenile idiopathic arthritis. *Pediatr Clin North Am* 2005;52:413-2.
11. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-2.
12. Rodríguez-Reyna TS, Martínez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. *World J Gastroenterol*. 2009;15:5517-4.
13. Mielants H, Veys EM, Cuvelier C, et al. Gut inflammation in children with late onset pauciarticular juvenile chronic arthritis and evolution to adult spondyloarthropathy-a prospective study. *J Rheumatol* 1993;20:1567-2.
14. Kokkonen J, Arvonen M, Vähäsalo P, et al. Intestinal immune activation in juvenile idiopathic arthritis and connective tissue disease. *Scand J Rheumatol*. 2007;36(5):386-9.
15. Arvonen M, Vähäsalo P, Turunen S, et al. Altered expression of intestinal human leucocyte antigen D-related and immune signalling molecules in juvenile idiopathic arthritis. *Clin Exp Immunol*. 2012;170(3):266-3.
16. Arvonen M, Ikni L, Augustin M, et al. Increase of duodenal and ileal mucosal cytotoxic lymphocytes in juvenile idiopathic arthritis. *Clin Exp Rheumatol*. 2010;(1):128-4.
17. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31:390-2.
18. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. First International Gastrointestinal Eosinophil Research Symposium

- (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; 133:1342–1363.
19. Okpara N, Aswad B, Baffy G. Eosinophilic colitis. *World J Gastroenterol* 2009; 15:2975–2979.
 20. Mutalib M, Blackstock S, Evans V, et al. Eosinophilic gastrointestinal disease and inflammatory bowel disease in children: is it a disease continuum? *Eur J Gastroenterol Hepatol*. 2015;27(1):20-3.
 21. Tabbers MM1, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58(2):258-74.
 22. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. *Best Pract Res Clin Rheumatol* 2006;20:451-1.
 23. Mielants H, Veys EM, Cuvelier C, et al. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. *J Rheumatol* 1995;22:2279-4.
 24. Saurenmann RK, Levin AV, Feldman BM, et al. Risk factors for development of uveitis differ between girls and boys with juvenile idiopathic arthritis. *Arthritis Rheum*. 2010;62(6):1824-8.
 25. Brakenhoff LK, van der Heijde DM, Hommes DW, et al. The joint-gut axis in inflammatory bowel diseases. *J Crohns Colitis*. 2010;4(3):257-8.
 26. Brakenhoff LK, van der Heijde DM, Hommes DW. IBD and arthropathies: a practical approach to its diagnosis and management. *Gut*. 2011;60(10):1426-5.

27. Stoll ML, Kumar R, Morrow CD, Lefkowitz EJ, Cui X, Genin A, Cron RQ, Elson CO. Altered microbiota associated with abnormal humoral immune responses to commensal organisms in enthesitis-related arthritis. *Arthritis Res Ther.* 2014;16(6):486.
28. Mielants H, Veys EM, Cuvelier C, et al. The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. *J Rheumatol* 1995;22:2273-8.
29. Cuvelier C, Barbatis C, Mielants H, et al. Histopathology of intestinal inflammation related to reactive arthritis. *Gut* 1987;28:394-1.
30. Medina PM, Novales VG, Medina PA, et al. Eosinophilic gastroenteritis associated with rheumatoid arthritis. Its presentation as acute abdominal pain. *Rev Esp Enferm Dig* 1997;89:143-4.
31. Ng WF, Cohen P, Hepburn A, et al. A case of eosinophilic enteritis and rheumatoid arthritis. *Rheumatology (Oxford)* 2005;44:1585-6.
32. Odze RD, Wershil BK, Leichtner AM, et al. Allergic colitis in infants. *J Pediatr* 1995;126:163-0.
33. Odze RD, Bines J, Leichtner AM, et al. Allergic proctocolitis in infants: a prospective clinico- pathologic biopsy study. *Hum Pathol* 1993;24:668-4.
34. DeBrosse CW, Case JW, Putnam PE, et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 2006;9:210-8.
35. Masterson JC, Furuta GT, Lee JJ. Update on clinical and immunological features of eosinophilic gastrointestinal diseases. *Curr Opin Gastroenterol.* 2011 27:515-2.
36. Demetter P, Baeten D, De KF, et al. Subclinical gut inflammation in

spondyloarthropathy patients is associated with upregulation of the E-cadherin/catenin complex. *Ann Rheum Dis* 2000;59:211-6.

37. Hommel KA, Franciosi JP, Gray WN, et al. Behavioral functioning and treatment adherence in pediatric eosinophilic gastrointestinal disorders. *Pediatr Allergy Immunol.* 2012;23:494-9.

38. Lucendo AJ. Eosinophilic diseases of the gastrointestinal tract *Scandinavian Journal of Gastroenterology*, 2010; 45:1013–1.

FIGURE LEGEND

Figure 1.

Photomicrographs of colonic mucosal biopsies from children with JIA

TABLE Legend

Table 1.

Demographics at endoscopy

Table 2.

JIA patients with abnormal gut histology, JIA types, gastrointestinal symptoms and treatment