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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

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Enteropathic Spondyloarthritis

GRADUATE THESIS

Zagreb, 2016.

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ABBREVIATIONS

APC	antigen presenting cells
AS	ankylosing spondylitis
axSpA	axial spondyloarthritis
CD	Crohn's disease
CRP	C-reactive protein
DMARD	disease-modifying antirheumatic drugs
EA	enteropathic spondyloarthritis
EIM	extraintestinal manifestations
ESR	erythrocyte sedimentation rate
HLA	human leukocyte antigen
IBD	inflammatory bowel diseases
IFN γ	interferon gamma
IL	interleukin
MDP	muramyl dipeptide
NOD2/CARD15	nucleotide-binding oligomerization domain-containing protein 2 / caspase recruitment domain-containing protein 15
NSAID	nonsteroidal anti-inflammatory drugs
RF	rheumatoid factor
SpA	spondyloarthritis
TNF	tumor necrosis factor
UC	ulcerative colitis

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SUMMARY

ENTEROPATHIC SPONDYLOARTHRITIS

Fanika Mrsić

The inflammatory bowel diseases are chronic idiopathic inflammatory diseases of the gastrointestinal tract that may be complicated by a variety of extraintestinal manifestations such as primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, acute anterior uveitis, and aortic insufficiency. However, rheumatological manifestations are the most common with spondyloarthritis being the most prevalent one. Enteropathic spondyloarthritis can present before, be synchronous with, or after the diagnosis of inflammatory bowel disease with two subsets of joint involvement: axial and peripheral. It is believed that genetic, immunological and environmental factors play a crucial role in the development of enteropathic spondyloarthritis. Although the association between extraintestinal manifestations of symptoms coupled with inflammatory bowel disease have been recognized from before, the exact pathogenic mechanism and link between articular and gut involvement is still largely unknown.

Functional studies in this particular field are still needed to understand the complex immune mechanism for these interrelated conditions in the future.

Early recognition of enteropathic spondyloarthritis in inflammatory bowel disease patients requires a multidisciplinary approach in order to guide therapy, reduce morbidity, prevent future disability and to improve the quality of life in the affected patients.

KEY WORDS: inflammatory bowel disease, extraintestinal manifestation, enteropathic arthritis, multidisciplinary approach

1. INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) that can be associated with joint disease as an extraintestinal manifestation (EIM) (1). Enteropathic spondyloarthritis (EA) is the most common and underestimated EIM in patients with IBD. EA belongs to the group of spondyloarthritis. The exact etiopathogenic mechanism and link between articular and gut involvement is still unknown.

1.1 SPONDYLOARTHRITIS

Seronegative spondyloarthritides (SpA) are a heterogeneous group of chronic inflammatory rheumatologic diseases of unknown etiology. The predilection sites are the spine and joints. Most commonly, it is marked by the presence of spinal and peripheral joint oligoarthritis, inflammation of sacroiliac joints and tendon attachments. For many patients, seronegative SpA does not only present with rheumatologic manifestations. Symptoms may occur elsewhere in the body including the heart valves, aorta, skin and eyes. A negative finding of rheumatoid factor (RF) and familial aggregation are something that diseases in this group have in common. The family of SpA encompasses a group of disorders that includes: ankylosing spondylitis (AS); psoriatic arthritis (PsA); reactive arthritis (ReA), known as Reiter's syndrome; enteropathic arthritis (associated with IBD, Whipple's disease, and "bypass" arthritis); and undifferentiated spondyloarthritis (uSpA).

The main representatives of this group of diseases are shown in Table 1 (2) and classification criteria for SpA diagnosis are shown in Table 2 (2).

Table 1. The entities of seronegative spondyloarthritis (*Modified according to Anić B, Babić-Naglić Đ, 2008)*

1. Ankylosing spondylitis
2. Psoriatic arthritis
3. Reactive arthritis (SARA and EARA, Reiter's syndrome)
4. Enteropathic arthritis (IBD, Whipple's diseases, "bypass" arthritis)
5. Undifferentiated spondyloarthritis

SARA – sexually acquired reactive arthritis; EARA – enterically acquired reactive arthritis

Table 2. Classification criteria for seronegative spondyloarthritis (*Modified according to Anić B, Babić-Naglić Đ, 2008*)

1. Asymmetrical peripheral arthritis
2. Negative RF finding
3. Absence of subcutaneous rheumatoid nodules
4. X-ray signs of sacroiliitis with or without ankylosis
5. Clinical overlap of symptoms of some diseases in this group (≥ 2 at the same time)
6. Family history
7. The presence of HLA B27 antigen

The prevalence of the SpA group as defined by the European Spondyloarthropathy Study Group (ESSG) criteria has been reported in the ranges of 0.3 – 1.4% in Europe and the

United States (3,4). The occurrence of SpA among close relatives indicates a genetic predisposition in the development of the disease (2). A number of genetic factors have been investigated involving human leukocyte antigen (HLA) locus. The most frequently documented is HLA B27. Although the connection between HLA B27 antigen and the development of SpA is still not well understood and not all patients have a positive result for this antigen, a high incidence of HLA B27 was noted in SpA patients.

Given the heterogeneity of diseases and symptoms in this group, therapeutic strategies require a multidisciplinary approach. The therapeutic principle for subsets of SpA does not differ from other inflammatory arthropathies. Most often used are nonsteroidal antiinflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids. The most commonly used DMARDs are methotrexate, sulfasalazine, leflunomide and chloroquine. In the last several years, biological drugs represent a class of new drugs that are used in the treatment of SpA because of their proven immunosuppressive / anti-inflammatory and immunomodulatory effects. The main representatives of this group of drugs are inhibitors of tumor necrosis factor (TNF-α) as a targeted biological response modifier.

Given that SpA has been historically underdiagnosed and unrecognized, early diagnosis is still a major challenge for clinicians in their everyday work.

2. INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (IBD) are chronic idiopathic inflammatory diseases of the gastrointestinal tract that are comprised of heterogeneous disorders such as Crohn's disease (CD) and ulcerative colitis (UC), and to a lesser extent, indeterminate colitis and microscopic colitis. They have an unpredictable course and their incidence is rising in recent years. IBD are one of the most common chronic inflammatory diseases and overall as many as 1.4 million people in the United States and 2.2 million people in Europe suffer from these diseases (5) with a peak of incidence between 15 and 30 years of age (6). Etiology is not yet well known but it is likely multifactorial and results from the interaction of genetic and environmental factors. IBD can be complicated by a variety of extraintestinal manifestations with symptoms manifesting elsewhere in the gastrointestinal system such as hepatic and oral in addition to cutaneous, ocular and musculoskeletal systems.

2.1 CROHN'S DISEASE

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract of unknown etiology that can affect any part of the gastrointestinal tract. It most commonly affects the terminal ileum but has the potential to affect any part of the gastrointestinal tract from mouth to anus with its main feature of transmural inflammation. It is a lifelong disease with a variable clinical course characterized by frequent remissions, exacerbations and EIM. The genetic and environmental factors seem to play a role in the etiology of CD.

2.1.1 EPIDEMIOLOGY

The incidence of CD is 0,1-16/100 000 and has increased during the past few decades (7). The incidence in Croatia is up to 7/100 000 (8). It usually begins between the ages of 15 and 30. Studies show that genetics plays a big role in the development of CD. It is more frequent in women, Caucasians and in some families. Close relatives have a 10-15 times higher risk for disease development and family history is positive in 6-20% of CD patients (8). A recent 12-year study in Texas showed that Hispanics had a lower incidence (0.62/100,000) than African-Americans (1.83/100,000) or Caucasians (4.5/100,000). In that same study it was shown that African-Americans are more likely to develop CD that UC (9).

The only proven risk factor for the development of CD is smoking. Interestingly, it is a protective factor for UC. Various environmental factors and their role in the pathogenesis of CD have been investigated, but so far none of them has proven to be a definitive cause of CD. Some of the potential environmental factors are showed in Table 3 (8).

Table 3. Potential environmental factors associated with IBD *(Modified according to Vucelić B, Čuković-Čavka S, 2008)*

Smoking
Oral contraceptives
Early childhood factors (early cessation of breastfeeding, hygiene, infection)
Infections (*Mycobacterium paratuberculosis*, measles, rubella)
Appendectomy
Food (refined sugars, margarine, yeast, chocolate, Coca-Cola)

2.1.2 ETIOLOGY AND PATHOGENESIS

Despite many studies over the past few decades, the exact etiology is not yet clear. The inheritance is complex-polygenic with several genes and environmental factors involved. It is believed that the dysregulated immune response to luminal bacteria in a genetically susceptible host is responsible for the development of CD. This means that genetics have an important if not decisive role in CD pathogenesis, as studies have shown.

The first susceptibility gene for CD that was identified was nucleotide-binding oligomerization domain-containing protein 2 also known as caspase recruitment domain-containing protein 15 (NOD2/CARD15) located on chromosome 16 (10). It is involved in recognizing bacterial muramyl dipeptide (MDP) and stimulating the immune system to respond properly. Mutation of NOD2 leads to the inappropriate recognition of bacterial intestinal flora and with inadequate immunological response results in an inflammatory state. The precise mechanism by which the NOD2 mutations lead to inflammation is not quite clear but this discovery and NOD2 association with CD was highly significant for supporting the hypothesis in which CD-affected patients have an abnormal response to intestinal bacteria. Other genes that have been identified as important in the development of the disease are DLG5, OCTN1 and 2, TLR4, IL23R, ATG16L1, DRB*0301 (8). Many studies are investigating CD-associated gene changes and those results are important to determine how those genetic variations are related to a person's chance of developing CD.

Abnormal intestinal permeability is another part associated with CD development. After bacteria are presented to antigen-presenting cells (APC) with subsequent antigen expression, T cells are activated resulting in an inflammatory state. Therefore, the Th1

response is predominant in CD with interferon gamma (IFNγ), TNFα and IL-12 as the main inflammatory mediators (8).

Observation of an increase in the incidence of IBD and its association with improvements in hygiene in the 20th century has led to the hygiene hypothesis. It claims that children raised in a more sanitary environment are more likely to develop CD in comparison to those exposed to enteric pathogens in their early childhood (11). Multiple factors such as *Helicobater pylori* exposure, helminths, antibiotic use, measles infection and vaccination, domestic hygiene and breastfeeding have been implicated in this theory (11). For now, the accuracy of the hygiene hypothesis is not confirmed and further studies in this area are needed to understand the potential mechanisms underlying the hygiene hypothesis and associations with IBD.

As can be seen, despite many various studies, the exact pathogenesis of CD is not yet fully known. It seems that inheritance is not enough for disease development but many explored, but also unexplored environmental factors are involved in the pathogenesis of CD. There is a strong need for future studies and researches in this area in the hope of understanding the mechanism and etiology of this disease.

2.1.3 CLINICAL PICTURE

The clinical picture is complex since CD can affect any part of the gastrointestinal tract, from mouth to anus. 75% of patients have the small intestine affected of which 90% have the terminal ileum affected (8). The rectum is usually spared. Changes in the gut include cryptal inflammation and abscesses, granulomas, fibrostenotic and inflammatory strictures.

The inflammation is transmural, involving the entire thickness of the intestinal wall with classical “skip lesions”. Transmural inflammation leads to the formation of a fistula between the bowel walls (enteroenteral), as well as between the bowel and vagina or the bladder (rectovaginal or enterovesicular, respectively). Narrowing of the intestine due to transmural inflammation leads to the characteristic spasms in the abdomen and possibly to the formation of intra-abdominal abscesses. The most prominent symptoms of CD are diarrhea, abdominal pain, weight loss, fatigue and bloody stools. Except intestinal symptoms, CD can manifest outside the gastrointestinal tract. EIM are not uncommon in CD patients (8). Some of them that are correlated with the intensity of bowel inflammation are arthritis, erythema nodosum, pyoderma gangrenosum and episcleritis. Others, such as primary sclerosing cholangitis, SpA and uveitis are not associated with IBD activity (8). CD can be complicated by various conditions depending on which part of the intestine is affected. Some of CD associated complications are sideropenic anemia, leukocytosis, disseminated intravascular coagulopathy, pyelonephritis, hydronephrosis, urolithiasis, thromboembolism and hypokalemic nephropathy. If the terminal ileum is affected, the place where vitamin B12 is absorbed, megaloblastic anemia can develop.

Also, if the CD affects the jejunum, patients have the potential to develop malabsorption syndrome.

To assess the disease and its inflammatory activity, clinicians can use many composite clinical indices available for everyday use. Some of them are the CDAI (Crohn's disease activity index), pediatric CDAI, Oxford Index, Cape Town Index, Harvey-Bradshaw Index etc. However, the most commonly used is CDAI (8,12).

2.1.4 DIFFERENTIAL DIAGNOSIS

As CD is a complex disease with very varied symptomatology, the differential diagnosis of CD includes many similar conditions. It is important to bear in mind all the possible differential diagnoses in order to detect the disease in a timely fashion and began treatment as soon as possible.

Diseases whose clinical picture can mimic the picture CD are infections (*Salmonella spp., Shigella spp., Campylobacter spp., Escherichia coli, Clostridium difficile*), intestinal ischemia and vasculitis, malignant diseases (lymphoma, leukemia, adenocarcinoma), medication-induced colitis, celiac disease, appendicitis, diverticulitis. Those are just some of the potential diseases that one should think of given that many diseases have a similar clinical picture and symptoms as CD.

2.1.5 DIAGNOSIS

Since there is no pathognomonic diagnostic test that could help us confirm the diagnosis of CD, the diagnosis of Crohn's disease can sometimes be challenging as it is based on the clinical presentation and on certain diagnostic tests.

A complete blood count is used to evaluate the inflammatory disease activity. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen are increased. In an active disease state, increased liver enzymes, hypoalbuminemia, leukocytosis, thrombocytosis and anemia can be found.

To exclude specific pathogens and inflammation of the gastrointestinal tract as a possible cause of disease, a stool analysis can be done.

The gold standard for the diagnosis of IBD is a gross inspection of the gastrointestinal tract that includes colonoscopy, esophagogastroduodenoscopy and in some cases capsule endoscopy. It is important to note that colonoscopy is contraindicated in the acute phase of the disease, in toxic megacolon, and when extensive fistulas are present. In addition to endoscopy, histopathological analysis of biopsy material is of great importance.

Radiological imaging methods that are useful for locating affected regions of inflamed bowel and intraabdominal complications are an abdominal ultrasound (US) and computed tomography (CT). In order to evaluate and detect complex perianal disease, magnetic resonance imaging (MRI) is the method of choice (8). X-ray of the abdomen is of great importance in excluding toxic megacolon, ileus and perforation. Barium enema, on the other hand, is useful in detecting complications and evaluation of the entire colon when strictures of the colon do not permit the colonoscope to pass through.

A small bowel follow-through is useful when the disease involves only the small intestine because colonoscopy and gastroscopy cannot be used to evaluate the entire small intestine.

2.1.6 TREATMENT

The treatment of CD is determined by the activity, severity, location, and type of inflammation taking into account the previous response, complications and presence of EIM. Some of the drugs used are the aminosalicylates which are represented by mesalazine in the form of azo conjugates, delayed-release formulations or enema. For active disease or relapse, systemic glucocorticoids such as prednisone, prednisolone, methylprednisolone or hydrocortisone can be used but not for the maintenance of remission. Prolonged use of glucocorticoids has significant side-effects. As a result, they are, in general, not used for long-term treatment. Immunomodulatory drugs (azathioprine, 6-mercaptopurine, methotrexate) are another option in the treatment of CD. Mostly, they are used in glucocorticoid resistant or dependent patients or when extensive disease is present (8). Additionally, they are effective in the maintenance of stable remission. For the treatment of sepsis and perianal disease, antibiotics can be applied, metronidazole and ciprofloxacin are the most common used ones.

In the last few years, advancing knowledge regarding the biology of chronic inflammation has led to the development of drugs with targeted action towards certain molecules involved in the inflammatory response. This so called biological therapy is used to treat active, refractory CD and CD associated EIM. Some of TNF-α inhibitors used in the treatment of IBD are infliximab, adalimumab, golimumab, certolizumab

pegol. A new drug, vedolizumab, is showing some promising results in the treatment of patients who showed no improvement on anti-TNF therapy (13).

However, more studies and data are needed for vedolizumab to be included as a treatment option for IBD. Biological therapy has an important role in the treatment of IBD patients but still there are some concerns regarding its safety profile, especially when they are applied as long-term maintenance therapy (14).

2.2 ULCERATIVE COLITIS

UC is a lifelong idiopathic chronic inflammatory disease of the gastrointestinal tract that belongs to the group of IBD. It is an intermittent disease characterized by frequent remissions and relapses with continuous mucosal inflammation of colon, affecting the rectum and spreading proximally in a continuous and concentric manner.

2.2.1 EPIDEMIOLOGY

A higher incidence is observed in developed countries with 0.6-24.5/100 000 and in the past few decades it has been stable (8). It is more common in men and begins most often between the ages of 20 and 40 with a second small peak in incidence in people after the fifth decade of life. An appendectomy prior to the age of 20 and smoking, in contrast to CD, are protective factors against development of UC.

2.2.2 PATHOPHYSIOLOGY

The exact etiology is unknown. As in CD, the interaction of genetic and environmental factors play a role in its pathogenesis. The predominant type of response in UC is Th2

with production of IL-4, IL-5, IL-6, IL-10 and IL-13 (8). A number of antibodies have been described in patients with UC, of which the atypical perinuclear antineutrophil cytoplasmatic antibodies (pANCAs) are the best known. Positive pANCA serology is found in approximately 50–60% of patients (15). However, the sensitivity of pANCA is not so high to be used as a diagnostic tool. It can only help us to differentiate UC from CD.

Certain genes have been associated with UC and some of them are HLA region, IL23R, DLG5, MDR-1, TLR genes and JAK/STAT pathway. All those results suggest that UC is a complex multifactorial and polygenic disease that leads to aberrant immunological response in genetically susceptible people.

2.2.3 PATHOLOGY

UC is characterized by an inflammation that is limited to the mucosa and submucosa. It begins in the rectum and extends proximally in a continuous pattern along the colon. The inflamed mucosa is red, granulated with spontaneous bleeding and ulcerations around which are islands of preserved mucosa. Not so uncommon are pseudopolips due to previous inflammatory conditions. The pathology in UC typically involves the distortion of crypt architecture, inflammation of crypts, crypt abscesses and mucin depletion. At a later stage of the disease due to recurrent attacks, various complications such as shortening of the intestines and toxic megacolon can occur.

2.2.4 CLINICAL PICTURE

Since UC is restricted to the colon, the symptoms depend on the extent of the disease and inflammation. The primary presenting symptom of ulcerative colitis is bloody stools, reported by more than 90% of patients (15). Usually, the stool is mixed with mucus and pus. Patients also report diarrhea, tenesmus, urgency, occasionally severe constipation and crampy abdominal pain, or ache over the left iliac fossa prior to and relieved by defecation. UC is associated with a general inflammatory process that affects many parts of the body. EIM, especially an axial or peripheral arthropathy, episcleritis, erythema nodosum and pyoderma gangrenosum may be present in 10% of UC patients (16).

2.2.5 CLASSIFICATION

It is recommended for UC to be classified according to disease extent since the extent of UC will influence the treatment modality and determine if oral and/or topical therapy will be applied. For instance, topical therapy in the form of suppositories or enemas is often the first line choice for distal disease, but oral therapy is appropriate for extensive colitis. For the assessment of disease activity we use several clinical indices of which the most commonly used one in daily practice is Truelove and Witt's criteria (8). This index defines UC as mild, moderate or severe based on some clinical factors such as temperature, pulse, CRP, ESR, bloody stools and hemoglobin. Truelove and Witts' severity index is shown in Table 4 (17).

Table 4. Disease activity in ulcerative colitis *(Adapted from Truelove and Witts)*

	Mild	Moderate	Severe
Bloody stools/day	<4	≥4	≥6 and
ESR	<20 mm/h	≤30 mm/h	>30 mm/h or
CRP	Normal	≤30 mg/L	>30 mg/L or
Hemoglobin	>11.5 g/dL	≥10.5 g/dL	<10.5 g/dL or
Pulse	<90 bpm	≤90 bpm	>90 bpm or
Temperature	<37.5 °C	≤37.8 °C	>37.8 °C

2.2.6 DIFFERENTIAL DIAGNOSIS

Many diseases have similar symptoms to UC and can present in a similar manner. The differential diagnosis described for CD is the same as for UC.

2.2.7 DIAGNOSIS

Given that the gold standard for the diagnosis of UC is not available, the diagnosis should be based on a combination of medical history, clinical evaluation, endoscopic and histological findings.

The diagnostic workup we use in the diagnosis of UC is similar if not the same as in CD. This includes: laboratory analysis, endoscopy, radiological and histopathological analysis. The best test for the diagnosis of ulcerative colitis is still endoscopy, most commonly rectoscopy. To assess the extent of the disease usually colonoscopy, capsule endoscopy and esophagogastroduodenoscopy are used.

2.2.8 TREATMENT

The treatment of UC may be mainly pharmacological or surgical. The goal is to induce remission followed by maintenance and to prevent a relapse of the disease. Treatment depends on the disease activity and severity. For distal disease (proctitis, proctosigmoiditis) topical therapy is applied. First –line treatment is topical mesalazine with or without oral mesalazine. For those patients who are nontolerant to aminosalicylates, glucocorticoids as second-line therapy can be prescribed. Treatment of extensive disease requires oral aminosalicylates/glucocorticoids or i.v. hydrocortisone/ methylprednisolone in the case of left-sided colitis and severe colitis, respectively. Mesalazine, aminosalicylates and 6-mercaptopurine are used for the maintenance of remission.

Unlike in CD, UC can generally be cured by surgery. The procedure is proctocolectomy with ileoanal anastomosis. It is necessary in the event of extensive hemorrhage, frank perforation, toxic megacolon, resistant fulminant colitis nonresponsive to therapy, colon cancer or in severe hemolytic anemia.

3. ENTEROPATHIC SPONDYLOARTHRITIS

Enteropathic spondyloarthritis or enteroarthritis (EA) is a nonerosive oligoarticular episodic migrating peripheral arthritis that belongs to a group of seronegative spondyloarthritides which occur in patients with IBD and other gastrointestinal disorders such as Whipple's disease and after intestinal bypass surgery.

3.1 HISTORY

A relationship between joints and bowel was first reported by Smith in 1922. He described an improvement of articular symptoms in rheumatoid arthritis (RA) patients who underwent colectomy (18). Later on, in 1929 and in 1935 Bargen et al. and Hench respectively, reported the arthritis tendency to flare upon exacerbation of colitis and to recede with remission of the intestinal symptoms (19). Although the occurrence of sacroiliitis in IBD patients was described by some authors in the 1950s, it was not until 1964, that the American Rheumatism Association recognized and classified arthritis associated with IBD as an independent clinical form (20) and this marked the turning point in the earlier understanding of that disease. A further study of joint and bowel relationship was postulated by Wright and Moll who included EA in the SpA group (21).

3.2 EPIDEMIOLOGY

Establishing the true prevalence of EA is challenging due to the use of different diagnostic criteria, methodological approaches, the difference in study design and sampling methods, the frequency of IBD in different geographic areas and the variability in the prevalence of HLA-B27 among different racial groups.

The prevalence of EA according to the Italian population is 0.09% and 0.02% according to a Swedish study (22). EA occurs most frequently between the ages of 25 and 50 and equally in both sexes, however, somewhat more often in men (8).

Rheumatologic findings are more frequent in patients with disease confined to the colon (23). 60-70% of patients with SpA have gut inflammation. Spinal or articular manifestations occur in 5%-20% of IBD patients. Arthritis and sacroiliitis are found in 10-20% patients and spondylitis in 10% of patients with IBD. Women tend to have more frequent peripheral joint involvement while men tend to have more axial joint involvement (24,25).

Sacroiliitis and spondylitis are associated with HLA B27 (40% and 60% respectively) but to a lesser degree than in uncomplicated AS (90%). Peripheral arthritis showed no connection with HLA B27. Potential risk factors for EA development are active bowel disease, family history of IBD, appendectomy, smoking and the presence of other EIM (26,27).

3.3 ETIOLOGY

The exact etiology of EA is still not fully understood despite many studies being conducted over the past decade.

It is believed that the combination and interaction of genetic, immune factors and bacterial gut infections play an important role in the emergence and development of the disease with environmental factors having a causative role in triggering the onset of the disease. Current theories suggest that aberrant migration of intestinal lymphocytes and macrophages from inflamed gut mucosa to joints in genetically susceptible people leads

to an abnormal state and immunological intolerance due to dysfunctional interaction of the immune system and gut bacteria (19,28).

IBD and SpA show familial clustering and may coexist in a patient. Various epidemiological studies have described the role of the HLA system in the development of EA. Among the genetic factors, the most studied one is HLA- B27 and it has shown the strongest genetic association with SpA being present in >90% of patients with AS in contrast to only 5-15% prevalence in the general population (29). It has more than 30 subtypes that differ by only single amino acids. Only a few of those subtypes are associated with AS (e.g. HLA-B*2705, HLA-B*2702, HLA-B*2704 and HLA-B*2707) (30). The 4 main theories that describe its role in the pathogenesis of AS are shown in Table 5 (30).

Table 5. Theories on the pathogenesis of SpA related HLA- B27 *(Modified according to Voulgari PV,2011)*

1. The arthritogenic peptide hypothesis
2. Alteration of intracellular handling of microbes
3. Recognition of HLA-B27 as an autoantigen
4. Self-association of the HLA-B27 molecule

One theory suggests that HLA-B27-expressing macrophages bind a set of antigenic peptides. They then expose the bacterial antigens and activate the T-cell response with migration of T –cells from the gut to the joint leading to the development of arthritis (31).

The second theory proposes that HLA-B27 leads to a less effective elimination of microbes with upregulation of pro-inflammatory cytokines.

Another, the third theory, also known as the molecular mimicry hypothesis, represents the sequence homology between HLA-B27 and bacterial antigens where HLA-B27 is presented by HLA class II heterodimers and recognized by CD4+ T- cells as an autoantigen. Because of this peptide homology, activation of T-cells by the mimicry mechanism leads to an inflammatory state.

The most recent theory, the self-association of HLA-B27 molecule, is based on endoplasmic reticulum stress. The production of inflammatory cytokines is induced by misfolding of the heavy chains of HLA-B27 within the endoplasmic reticulum because the folding process of HLA-B27 heavy chains is slower than that of other HLA alleles. Accumulation of misfolded proteins results in chronic inflammation due to activation of the endoplasmic reticulum-unfolded-protein-response and nuclear factor κB (NFκB). Also, those B27 homodimers can be expressed on the cell surface and act as antigens producing an auto-inflammatory response without the need for antigen or by migration to cell surface HLA-B27 present peptides to other inflammatory cells.

To conclude, the association of HLA-B27 with SpA-associated IBD is still higher than in the IBD population without SpA, and therefore, HLA-B27 in IBD patients seems to increase the risk of EA development (32).

In addition to HLA-B27, other genes have been documented as being related to SpA and IBD. The genome scans have identified potential susceptibility genes that might have a role in the pathogenesis of SpA and IBD. The most prominent association documented was with IL-23 receptor polymorphism (33). It was shown that IL-23 is the only

susceptible gene shared by SpA and IBD so far. Its functional role is still not clearly defined but it is associated with an increased risk of developing AS and IBD. Binding of IL-23 to its receptor activates various signaling molecules and the production of cytokines (34).

Loss of homeostasis between regulatory T-cells (T_{reg}) and proinflammatory Th17 cells can also lead to an aberrant immune response. Reduced ratio of T_{reg} to Th17 cells creates a proinflammatory environment, supporting the expansion and expression of Th17 cells (35). Interestingly, a connection between IL-23 and Th17 was established. Although the role of IL-23 is still unclear, it is believed that IL-23 signaling has a role in inflammation, mediated by Th17, by promoting expression and production of IL-17, IL-22 and TNF-α, indicating that Th17 could represent a common pathogenic mechanism in the development of both SpA and IBD (19, 34). This new pathway: IL-23/IL-17 axis is a potential treatment target for EA and can be a valuable addition to the currently available treatment of IBD-associated spondyloarthritis.

NOD2/CARD15, also called inflammatory bowel disease protein 1, is another protein that plays an important role in the immune system and the development of CD. Its main function is to detect bacterial antigen and stimulate an appropriate immune reaction against it. The mutation of CARD15 results in inappropriate bacterial elimination and disrupts the protein's ability to recognize and respond to microbial challenges. CARD15 is seen in increased concentrations in AS patients with developed IBD (36,37) but studies have not shown its association with primary AS. Therefore, mutation of CARD15 is for now, considered a risk factor for bowel inflammation in SpA patients although its role in the process of intestinal bacteria presentation remains unclear.

To summarize, IL23 receptor is the only identified susceptibility gene and first common risk gene for primary AS, UC and CD, unlike CARD15, a risk factor for CD in SpA, which does not appear to define the overall disease susceptibility (38). As we can see, many studies have investigated the role of various genes in the pathogenesis of SpA and IBD in order to try to explain the interaction of those two complex diseases. Still, not enough is known and further studies are needed to detect the genetic component shared by these interconnected diseases.

Altered barrier function of the gastrointestinal tract and the subsequent increase in intestinal permeability, allowing gut bacteria or antigens to interact with the immune system, results in entry of gut bacteria into the subepithelial layer and inflammation of the gut (39). Altered permeability has been demonstrated in patients with both SpA and their healthy first- degree relatives. Some studies showed an increase in small intestine permeability in rheumatoid arthritis, SpA and IBD patients although other studies have failed to reach the same result (40,41). Because of this, the role of gut inflammation in the pathogenesis of Spa and IBD has yet to be proven.

The proposed mechanism and the role of the gut permeability in pathogenesis of SpA and IBD is as follows: disturbance of the barrier function in the gastrointestinal system leads to gut microbiota changes and gut inflammation. In such chronic inflammatory conditions, APC cells present antigens to naïve T-cells which continuously circulate between lymphoid tissue and blood. Upon encounter with the antigens, T-cells proliferate, differentiate and reach the site of inflammation by means of CCR9 and CCL25 (39). Under the influence of cytokines, other endothelial cells express VAP-1, VCAM-1 and ICAM which then bind to the activated T-cells. Salmi et al. (42) discovered

that VAP-1 is expressed preferentially in inflamed synovial tissue and supports binding of all leukocytes. Additional adhesion molecules such as VCAM-1 and ICAM that are present in the small intestine also adhere to synovial vessels. Once the mucosa is breached, T-cell tolerance to normal gut microbiota is damaged. Activated T-cells from the intestinal mucosa through the systemic circulation enter the joints and generate a specific immune response against the synovium causing an inflammatory state there as well. It was shown that lymphocytes from the gut of IBD patients are ten times more capable of binding to the synovium as compared to healthy controls. Given that, altered trafficking of gut lymphocytes might be another contributable factor in the immunopathogenesis of EA as a connection between IBD and SpA development. Microbiota of the gut refers to the ecological community of commensal, symbiotic and pathogenic microorganisms within an individual. The human gastrointestinal system harbors extremely complex microbiota with more than thousands of different bacterial species that increase in number from the stomach to the colon reaching its maximum numbers in the colon i.e.10^{11}-10^{12} CFU/ml of luminal content. Dominant bacteria in the small intestine are the facultative anaerobes, whereas in the large intestines it is the obligate bacteria (39). This community of living microorganisms is stable throughout life and continuous host-bacterial interaction aids in food digestion and absorption and in the production of metabolites. Commensals provide a protective role to the host by preventing adherence of pathogenic bacteria to the mucosal layer, regulation of epithelial proliferation and maintenance of immune homeostasis. Because of this huge antigenic load present in the gastrointestinal tract, the immune system has to continuously communicate with the gut bacteria to prevent an aberrant state of inflammation by

constantly downregulating mucosal immune cells (43). This process is known as “oral tolerance”. Previous studies suggested that enteric commensals can be an environmental trigger of AS in genetically susceptible people and that loss of immune tolerance can lead to chronic inflammation (44). With further investigations, several species have been recognized as potential causes in the pathogenesis of SpA and IBD. Some of them are: *Bacteroides vulgatus*, *Klebsiella pneumoniae, Disulfovibrio disulfuricans*, *Salmonella spp., Campylobacter spp*. and *Yersinia enterocolitica*. As previously mentioned, bacteria from the circulation can lodge in the joints with the uptake being more pronounced when arthritis is present. The presence of bacterial components within synovial joints was an interesting finding since the joint was assumed to be a sterile environment (45). Bacterial antigens have been isolated in joints of affected people indicating that bacteria and their antigens can play an important role in initiating arthritis when gut inflammation is present. Confirming this theory, HLA-B27 transgenic animal models have also shown the role of normal gut flora in the pathogenesis of SpA. These rats have spontaneously developed a colitis and axial and peripheral arthritis. Surprisingly, when kept in a germ-free environment, these rats were protected from gut and joint inflammation. Furthermore, on exposure to gut bacteria, especially *Bacteroides spp*. colitis and arthritis developed in 83% by 3 months (44). Thus, it appears that bacteria are important factor in the pathogenesis of both SpA and IBD due to their interaction with the host’s immune system.

To conclude, the exact pathogenetic autoimmune mechanism of EA is still not defined. SpA and IBD share many genetic and pathogenic features. Many studies have been conducted showing that in genetically susceptible individuals, altered gut permeability,

bacterial antigens and various potential genes are implicated in the development of those two complexes diseases. Although SpA and IBD share many risk genes and immunological evidence for shared pathogenesis have increased our understanding of these two interrelated disorders, further molecular and functional studies are needed for providing us with the evidence of a common pathogenetic mechanism.

3.4 CLINICAL PICTURE

Articular complications are the most common EIM in IBD. Arthropathies associated with IBD belong to the SpA group of disorders. Arthritis can affect the spine, sacroiliac joint, peripheral joints, or a combination of these sites.

Joint involvement is divided by the Assessment in Spondyloarthritis International Society (ASAS) classification in two subsets: axial (including sacroiliitis with or without spondylitis) and peripheral (46). Peripheral or axial articular involvement can precede, be synchronous with, or develop following the diagnosis of IBD, often by as many as 10 years.

Diagnosis of axSpA is based on clinical features of inflammatory low back pain supported by radiological changes of sacroiliitis with the MRI being the diagnostic tool of choice. HLA-B27 is over-expressed in axSpA but it has a lower prevalence than in idiopathic AS; 25-75% versus 7-15% respectively; making it of no diagnostic value (47). The prevalence of axial involvement in IBD patients is 5-12%. It is more prevalent in men with male to female ratio of 3:1.

Axial involvement is more common in CD patients (5-22%) than in UC (2-6%) (48) and can precede the onset of enteritis by many years. University Health Network in Toronto

conducted a cohort study and results showed that 52% of IBD patients experienced bowel symptoms after the onset of SpA symptoms, 39% patients experienced symptoms prior to the onset of SpA and only 9% had bowel and SpA symptoms concurrently (49).

Symptoms generally are not synchronous with bowel activity and are independent of exacerbation of bowel inflammation. The main complaints are pain in the pelvis after rest with morning stiffness which is then relieved by movement, exacerbated by coughing and sneezing, persistent lower back pain usually before the age of 45 years with duration of at least 3 months (30,50). The clinical course is similar as in idiopathic AS with squaring of the vertebral bodies, marginal syndesmophytes and cervical spine immobility - ankylosis with classical presentation of the so-called “bamboo spine” (51).

Extra-axial manifestations of IBD-associated arthritis include peripheral arthritis, enthesitis, dactylitis, uveitis, and psoriasis.

Peripheral arthritis is an inflammatory arthropathy, RF–negative, nondeforming, and nonerosive. It is the most frequent finding in IBD patients (17-20%) (52) and it is more prevalent in CD (53). Arthritis occurs equally in males and females between the ages of 25 and 45 years and is generally more common in patients with colonic disease rather than those with small-bowel disease. In addition, arthritis is more common in CD with colonic involvement than UC and is more common in UC with pancolitis than isolated left-sided disease. (19,53)

Diagnosis is based on signs of inflammation and exclusion of other forms of arthritis (47).

Peripheral arthritis, occurring in 5–20% of IBD patients, classically involves large weight-bearing joints of the lower limbs (knees, ankles and metatarsophalangeal joints)

and presents as asymmetric monooligoarthritis. It is generally acute in onset with peak within 48 hours. The course is episodic, recurrent with spontaneous reduction within 6 months (19). A small percentage will go on to become a chronic form (10-20%) (38). Exacerbations follow the extent and severity of IBD and stable reduction was seen after colectomy (54).

The ASAS guidelines divided peripheral arthritis into oligo- or pauci-articular (type I) and poly-articular (type II) types.

Type I is a pauciarticular arthritis affecting fewer than 5 large joints. Occurring in approximately 3.6% of UC patients and 6% of CD patients (53). It is usually asymmetric, acute, self-limiting and associated with active bowel disease. On clinical examination, tender painful swollen joints are observed. It is generally migratory and transient without permanent joint damage. Type I is associated with HLA-DRB1*0103. This allele is found in 35% of type I patients in comparison to 3% of controls (55).

Type II is a polyarthritis (involving ≥ 5 joint) mainly affecting the small joints of the hand as a symmetrical, seronegative arthropathy. It affects 3-4% of IBD patients (30). Symptoms can last for months or years independent of IBD activity. It may persist after colectomy and exacerbations can continue for years (30,51). Diagnosis is based on the clinical picture and exclusion of other forms of arthritis. Type II is associated with HLA-B44* in 62% of patients in contrast to 30% of controls (55). Summary of type I and type II peripheral arthritis is shown in Table 6.

Table 6. Type I and Type II peripheral arthritis

	Type I	Type II
Joint involvement	<5 joints	≥5 joints
Pattern	Asymmetric	Symmetric
Acute/chronic	Acute	Chronic
IBD activity - associated	+	-
HLA region	HLA- DRB1*	HLA-B44*
Exacerbations	-	+
Limbs affected	Lower limbs	Upper limbs

3.5 DIFFERENTIAL DIAGNOSIS

The differential diagnosis of joint pain in patients with IBD is broad. Because EA is characterized by various clinical features that are not specific and pathognomonic for this entity, clinical signs must be differentiated from those of other SpA, rheumatoid arthritis and other connective tissue diseases. Due to overlap with some other rheumatological diseases, we also need to include secondary hypertrophic osteoarthropathy, glucocorticoid-associated osteonecrosis, and septic arthritis into our differential diagnosis. Similar symptoms and clinical picture of EA with ReA, sarcoidosis, "bypass"arthritis, Whipple's disease, Adamantiades-Behçet's disease and gluten sensitive enteropathy provide us with other differential diagnoses that must be taken into account when considering EA as the main disease.

3.6 DIAGNOSIS

The diagnosis of EA is based on the clinical presentation and linkage of rheumatologic and bowel symptoms together with the exclusion of other specific forms of arthritis. There is no pathognomonic finding that could lead us to the diagnosis of arthritis due to IBD and it is important to recognize IBD and its associated EIM. Most laboratory findings are also nonspecific. Usually they follow IBD activity and they don't have a major role in setting up a definitive diagnosis of EA. Anemia, as one of frequent findings in IBD patients reflects both iron deficiency anemia and anemia of chronic disease. Thrombocytosis and leukocytosis are also not uncommon findings in EA. Markers of inflammation such as ESR, CRP are increased but all those are nonspecific acute-phase reactants and are present in many other inflammatory states. RF and antinuclear antibodies as markers of inflammatory rheumatic diseases are negative. Analysis of synovial fluid and radiological findings are not characteristic. There are mild to marked inflammatory changes with white blood cells ranging from 1,500-50,000/mm^3. Glucose levels are not reduced and microbiologic cultures are negative (56). Nonspecific abnormalities are also seen while performing synovial membrane biopsy. Usually proliferation of synovial lining cells, increased vascularity with mononuclear cell infiltration is seen (30). It is important to exclude septic arthritis by joint aspiration because the clinical presentation in IBD patients can be atypical due to anti-inflammatory/immunosuppressive therapy that those patients are receiving.

According to European Crohn's and Colitis Organisation (ECCO), the diagnosis of axSpA is based on the clinical picture of inflammatory lower back pain associated with MRI or radiographic features of sacroiliitis. Radiologic evidence of sacroiliitis occurs in

20-50% of patients with UC and CD, but progressive ankylosing spondylitis occurs in only 1-10% of patients (47). MRI can identify early sacroiliitis in symptomatic patients with normal plain radiology.

The diagnosis of peripheral arthropathy and enthesitis associated with IBD is generally not accompanied by radiographic changes and is based on signs of inflammation and exclusion of other specific forms of arthritis (47).

To conclude, when diagnosing EA, clinical examination, laboratory and radiologic tests must be taken into account to obtain the broad picture of its interaction, coherence and integrity.

3.7 TREATMENT

Therapy of EA patients should include a rheumatologist and a gastroenterologist with their active cooperation in order to reduce inflammation and prevent disability or deformity.

When choosing a treatment, the therapeutic approach must be comprehensive and tailored to the requirements of the individual patient taking into account disease activity, clinical presentation and general condition of the patient, age, sex, comorbidities, and treatment which he or she is taking.

Non pharmacologic treatment includes rest and physical therapy. The goal of physical therapy is to maintain overall functional capacity of the patient, spinal mobility and to prevent deterioration and deformities of the spine that could lead to respiratory compromise and disability. Swimming, breathing exercises and medical gymnastics are

preferred as additional help to prevent possible unwanted consequences from developing (30).

Pharmacological treatment is primarily directed at the treatment of the underlying bowel disease. The use of analgesics, NSAIDs, DMARDs, glucocorticoids and anti-TNFα drugs is usually enough to treat most of the symptoms.

NSAIDs are prescribed to keep peripheral arthritis, back pain and stiffness under control. However, caution is necessary particularly in UC patients because of their potential effect on IBD exacerbation. Cyclooxygenase-2 selective inhibitors could be prescribed for EA patients because of their effects on epithelial proliferation and wound healing but their effect is of very limited value and in clinical practice is not often prescribed as a therapy for EA patients. In a recent study it was shown that Cox-2 selective agents may be better tolerated in the short term but their side effects such as cardiovascular toxicity limit their usage and overall benefit in EA (30). Despite the concerns about side effects and potential worsening of IBD, rheumatologists and gastroenterologists have used NSAIDs and Cox-2 inhibitors to good effect successfully in IBD patients with limited risk of exacerbating the bowel symptoms. However, if a clinical picture worsening is noticed, discontinuation of these drugs is advised.

Patients with axial SpA because of its potential disabling course, should be managed by a rheumatologist. Initial nonpharmacological approach is recommended in patients with axSpA. This includes physiotherapy and education. Usually, NSAIDs are used as a first-line therapy for stiffness and pain but only in the short term when they are well tolerated. Long term NSAID therapy should not be used as a treatment of axSpA (47). Although some studies have shown that high dose of NSAID are associated with an increase of

disease activity, the use of etoricoxib and celecoxib (COX-2 inhibitors) may even be safer with a lower risk of disease flaring when compared to conventional NSAIDs. Methotrexate and sulfasalazine are of limited efficiency and value in the treatment of SpA symptoms and literature does not support the use of DMARDs and systemic glucocorticoids for axSpA.

The induction of anti- TNFα agents as targeted biological response modifiers, had a major impact in the treatment of both IBD and axSpA. They should be used in order to reduce the progression of early nonradiologic axSpA in patients who are intolerant and refractory to NSAIDs or with some contraindications for NSAID use (57). The most widely used TNF-α inhibitors are infliximab and adalimumab. Both of these drugs are effective in IBD, axSpA and peripheral arthritis. Etanercept, another representative of the group, can control CD-associated arthritis but its effect on bowel disease itself is marginal. In the case of primary non-response or intolerance, switching to a second TNF-α inhibitor was shown to be beneficial. A pegylated humanized antibody (certolizumab) is approved in Switzerland as a drug for the treatment and maintenance of response in patients with moderate to severe CD who had an inadequate response to previously mentioned therapy. It is has not yet been approved by the European Medicines Agency but preliminary results show that certolizumab could be beneficial in patients who in the first place responded to infliximab but have over the time lost the response or become intolerant to it (30,58). Precaution measures should be taken as for all patients on anti-TNFα agents with skin test for tuberculosis and evaluation for latent infection prior to the initiation of the anti-TNFα therapy.

In patients with peripheral arthritis, the treatment of underlying gut inflammation is usually sufficient. Symptomatic relief with short term glucocorticoids, NSAIDs and local steroid injections has a proven effect. Oral glucocorticoids are effective but only in the short term and should be discontinued as soon as possible. When disease duration is short or ESR is increased, sulfasalazine can be used as therapy for IBD associated arthritis. Although some studies have shown that sulfasalazine was not superior to placebo (59), it is still optimal treatment in SpA patients with peripheral disease and in large joint arthropathy.

The main biologic agents used in IBD - associated arthritis are TNF-α inhibitors: infliximab, adalimumab, golimumab. They have been found to induce and maintain remission in persistent disease that affects the quality of life.

New biologic therapies have been investigated due to our better understanding of the genetics and pathogenesis of CD, UC and EA. One such example is vedolizumab that is effective in moderate-to-severe IBD but its effect on IBD-associated arthritis has yet to be studied (60). Some promising results were shown with inhibition of IL-12/23 and IL-17, ustekinumab and secukinumab, respectively. However, further studies are required to prove the effectiveness of new targeted therapies and their role in the future treatment of EA.

4. CONCLUSION

EA is a nonerosive oligoarticular episodic migrating peripheral arthritis that belongs to a group of seronegative spondyloarthritides which occurs in patients with IBD. The exact etiopathogenesis and the link between articular and gut involvement is not yet known but it is believed that the interaction of genetic, immune factors and bacterial gut infections play an important role in the emergence and development of the disease with environmental factors having a causative role in triggering the onset of disease. Many studies have been conducted showing that altered gut permeability, bacterial antigens and various genes are implicated in the development of EA in genetically susceptible people. Joint involvement in EA is classified in two subsets: axial and peripheral that can precede, be synchronous with, or develop following the diagnosis of IBD. Diagnosis is based on the clinical presentation, linkage of rheumatologic and bowel symptoms with exclusion of other specific forms of arthritis. Non pharmacologic treatment includes rest and physical therapy. Pharmacological treatment is primarily directed at the treatment of the underlying bowel disease. The use of analgesics, NSAIDs, DMARDs, glucocorticoids and anti-TNFα drugs is usually enough to treat most of the symptoms. The recognition of EA requires a multidisciplinary approach and active cooperation between rheumatologists and gastroenterologists in order to reduce inflammation, prevent deformity and worsening of quality of life in IBD patients.

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7. BIOGRAPHY

I was born on December 28th in Zagreb where I finished elementary school. I attended V. gimnazija and secondary music school Elly Bašić. I finished both primary and secondary school with honors. During the primary and secondary education I won awards several times in national and international competitions. In 2010, I enrolled in the Medical Studies in English program, where in 2014 I received the Dean's Commendation for distinguished success in the academic year 2013/2014. During my studies I was a demonstrator at the Department of Anatomy and at the Department for Internal Medicine, University Hospital Center Zagreb. I am a student representative and member of the eMED group. In 2016 I received Rector's award. During my studies I went to the Department for Hemato-oncology at the Katholische Karl-Leisner-Klinikum in Germany. I am fluent in both English and German and have a good knowledge of Spanish.