

Special Article

Inflammatory Bowel Disease and Infectious Factors

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Abstract

Purpose: The purpose of this study was to investigate the bibliography about the causes of infectious diseases in Inflammatory Bowel Disease (IBD) patients.

Material and Method: We searched databases (Pubmed and Cochrane) and we used articles of the last decade, studies, and researches related to the subject were examined.

Results: The aetiology of IBD remains largely unknown, although it is generally acknowledged that multiple factors are engaged leading to an array of intestinal and extraintestinal manifestations. The emergence of infections in IBD patients may be due to the underlying immunosuppression, which can also refuel formerly dormant opportunistic infections that could hinder the treatment of IBD and perhaps increase complications and mortality. Regarding the etiopathogenesis of IBD some infectious factors have been identified, especially regarding CD where atypical mycobacteria have been found in a few patients. Patients with Crohn's Disease and Ulcerative Colitis have been found to have increased concentration of Adherent-Invasive E. coli strains that tend to invade the intestinal epithelial cells by releasing large quantities of pro-inflammatory cytokines. IBD patients under treatment with corticosteroids, immunomodulating and biological agents, are classified as immunocompromised and in risk of developing infections. Those infections are caused by microorganisms that take advantage of the weakened immune system and lead to full infections, while under normal circumstances they would cause nothing or at most only minor infections.

Conclusions: IBD patients make up a priori a population with suppressed/compromised immune system. Those patients should be closely monitored for infections, including TB, before, during and after treatment with infliximab.

Key Words: Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease, Immunobiological factors, Surgical Infectious Disease

Introduction

The Inflammatory Bowel Disease (IBD) basically pertains to two diseases, namely Ulcerative Colitis (UC) and Crohn's Disease (CD), while in the middle ground there are cases that share common characteristics or have clinical, radiological or histological traits that disallow their classification in either category, until the course of the disease will allow a clearer classification (Loftus, 2004; Ng et al., 2017). The etiology of IBD remains largely unknown, although it is generally acknowledged that multiple factors are engaged leading to an array of intestinal and extraintestinal manifestations. Several environmental, genetic, microbial and immunological factors seem to play a role for the manifestation of these diseases.

Although several immunological phenomena have been described (e.g. increased cytokines or prostaglandins), nevertheless those may be not specific to the disease or secondary regarding the inflammation processes. Immunobiological factors are thought to play a role in IBD, the main cause being an immunodeficiency in the mucous membrane. There are indications that the adhesive forms of *Escherichia coli* may cause inflammation with the participation of lymphocytes (Bernstein and Shanahan, 2008; Molodecky and Kaplan, 2010).

The genetic predisposition for IBD may have to do with factors (glucoprotein) of the intestinal epithelium that interact with environmental factors causing a chronic inflammation. Several microbial factors have been examined with negative results regarding their role in causing inflammation, including the mycobacterium avium paratuberculosis. The number of patients diagnosed with IBD has increased worldwide in alarming rates, increasing IBD incidence rates as well. UC and CD frequency varies by region. UC incidence is between 4-14 new cases per 100 000 population annually and CD incidence is 1-10/100 000 persons. Both conditions are found more commonly in Caucasians rather than Black people, and are even more common in Jews (Ye et al., 2015; Burisch and Munkholm, 2015). In Europe, the incidence of the disease is higher in Northern Europe than Southern Europe. Also, it seems that UC is more common than CD in Europe, with the possible exception of Germany, France and Great Britain. Research also shows that UC has lower incidence in countries such as Greece, Hungary and Spain (Rubin et al., 2000;

Niriella et al., 2010; Katsanos et al., 2010; Katsanos et al., 2015).

The emergence of infections in IBD patients may be due to the underlying immunosuppression, which can also refuel formerly dormant opportunistic infections that could hinder the treatment of IBD and perhaps increase complications and mortality (Irving and Gibson, 2008).

The aim of this study was to investigate the bibliography about the causes of infectious diseases in IBD patients.

Infectious factors as IBD Etiopathogenesis

Regarding the etiopathogenesis of IBD some infectious factors have been identified, especially regarding CD where atypical mycobacteria have been found in a few patients. Several infectious factors are thought to be behind CD, such as the *Mycobacterium paratuberculosis*, paramyxovirus and measles virus and some types of the *Helicobacter pylori*. For UC, mutated *E. coli* stems and other microbial factors have been thought to play a role (Papadakis et al., 1999; Loftus, 2004). Those pathogens can trigger inflammatory reactions that cannot be controlled by the intestine's immune system. Inflammatory enteropathies usually go together with various immunologic problems that may be of pathogenic importance. Some factors that may indicate an intense immunological reaction, include increased number of IgG secreting cells, along with high numbers of cytotoxic CD-8 lymphocytes (Harrison, 2005).

UC and CD frequencies are not directly related to the frequency of infectious dysenteries. Even so, microbial infections remain as possible pathogenic mechanisms behind the disease, since there are inflammatory bowel diseases caused by well-known bacteria that cause enteritis and colitis, e.g. *Yersinia enterocolitica*, Non-O group 1 *Vibrio cholera*. Also, several inflammatory conditions of the intestines in animals that bear some similarities with non-specific bowel inflammatory conditions in humans, are caused by bacteria or viruses; more specifically, the suspicion that those two diseases may be caused by one or more viruses, came from the clinical similarity between UC and colitis caused by Lymphopathia-Venereum virus, as well as the experimental formation of enteritis after contamination with rotavirus.1,6,12 (Loftus,

2004; Katsanos et al., 2010; Burisch and Munkholm, 2015).

Infectious pathogenic factors in IBD

Several infectious factors have been thought to cause CD, such as the Mycobacterium paratuberculosis, paramyxovirus measles virus, and some types of the Helicobacter pylori. On the other hand, for UC some mutant E. coli strains along with various microbial products have been thought to play an important role^{6,7}. Those pathogens trigger inflammatory responses that the intestinal immune system cannot manage and control⁸. Patients with Crohn's Disease and Ulcerative Colitis have been found to have increased concentration of Adherent-Invasive E. coli (AIEC) strains that tend to invade the intestinal epithelial cells by releasing large quantities of pro-inflammatory cytokines (Conte et al., 2006; Baumgart et al., 2007). Crohn's disease patients have also increased concentrations of Proteobacteria and Bacteroidetes along with low concentrations of Clostridia compared to healthy persons and those suffering from UC (Gophna et al., 2006).

The frequencies of CD and UC are not directly linked to those of infectious dysenteries. Nevertheless, microbial infections remain a possible cause, mainly for the following reasons:

- There are inflammatory intestinal diseases caused by bacteria;
- New bacteria have been recognized to cause enteritis and colitis, e.g. Yersinia enterocolitica, Non-O group 1 Vibrio cholerae.
- Several inflammatory bowel conditions in animals that bear some resemblance to non-specific inflammatory bowel conditions in humans are caused by bacterial or viruses.

The suspicion that those two conditions may be caused by one or more viruses came from the clinical resemblance between UC and the colitis due to the Lymphopathia-Venereum virus, and the emergence of enteritis after contamination with rotavirus (Loftus, 2004; Burisch and Munkholm, 2015).

Infectious colitis

Infectious colitis, either primary or secondary, seems to be on a rise worldwide. It seems to be the cause of 211-375 million medical visits, 1.8 million hospital admissions and 3100 deaths

annually in the USA. In developed countries morbidity and mortality is usually with regard to paediatric patients or immunocompromised persons (DuPont, 2012, Navaneetha and Giannella, 2011).

The assessment of patients with infectious colitis is a diagnostic challenge, while the modes of transmission usually include food or water, thus the transmission is related to living conditions and socio-economical status, as well as seasonal distribution. The correlation between infectious colitis and IBD is mainly based on their many common clinical characteristics which call for rigorous differential diagnosis. The diagnosis of infectious colitis is mainly focused on finding the microbial factor behind the disease. The microbes that are more likely to cause infectious colitis are Campylobacter jejuni, E. coli, Salmonella, and Shigella species and C difficile, including many viruses (Jenkins et al., 1997).

The multiformity of the clinical appearance and its accompanying symptoms, such as fever, tenesmus and abdominal pain, may lead a physician towards IBD, especially if blood in the stool was present. When there are rectal changes caused by Chlamydia, resembling those characteristic of non-specific rectitis, they may lead to rectal stenosis and abscesses similar to those present in CD. Infectious colitis may involve into IBD, although rarely, since infectious colitis could appear as typical ulcerative colitis even after the disappearance of the microbe, the most common microbial factors being amoebas, shigella, salmonella, aeromonas and cytomegalovirus (Schwartz and Loftus, 2002; Leighton et al., 2006).

Risk of Infections in IBD patients

Immunosuppression

IBD patients under treatment with corticosteroids, immunomodulating and biological agents, are classified as immunocompromised and in risk of developing infections. Those infections are caused by microorganisms that take advantage of the weakened immune system and lead to full infections, while under normal circumstances they would cause nothing or at most only minor infections. Risk factors for developing infections include malnutrition, older age, primary immunodeficiency, HIV infection, chronic diseases, and use of corticosteroids,

immunomodulating agents, as well as anti-TNF therapy.

TNF α suppression may obscure infection symptoms like fever. The early recognition of the atypical clinical signs of serious infections, as well as those of typical yet more uncommon infections is important for minimizing delays in diagnosis and treatment. Patients under TNF inhibitors are more prone to serious infections. Patients under treatment with infliximab are also often found with TB, bacterial infections, including sepsis and pneumonia, intrusive fungal, viral or other infections. Some of those cases were lethal, whereas the most common opportunistic infections with mortality rates higher than 5%, include pneumocystosis, candidiasis, listeriosis and aspergillosis (Leighton et al., 2006; Burisch and Munkholm, 2015).

Viral infections

The infections of IBD patients include viral infections (herpes virus, human papillomavirus, influenza viruses, JC virus), bacterial ones (TBC, Clostridium difficile infection, pneumococcal infection, legionellosis, listeriosis), fungal infections (histoplasmosis, cryptococcosis, Pneumocystis jirovecii infection, aspergillosis, candidiasis) and finally parasitic infections (Strongyloides stercoralis infection), (Leighton et al., 2006; Burisch and Munkholm, 2015).

HCV and HBV infection

There have been cases of HCV infection and hepatitis B in IBD patients, mainly due to the use of immunomodulating drugs that indirectly rekindle the chronic disease (Li, et al., 2010; Ueno et al., 2005; Horn et al., 2009). Research shows that the prevalence of HCV infection is higher in IBD patients and even more so in younger CD patients. From the patients' history, it has been proposed that they contracted the virus via blood transfusion after surgery (Longo et al., 2000; Bronowicki et al., 2005). In case of HCV infection or hepatitis B in IBD patients under treatment with infliximab, the use of interferone should also be considered under close monitoring of the transaminases; moreover the concurrent treatment of hepatitis does not seem to interfere with the treatment of IBD. It goes without saying that HBV-negative patients with IBD should be vaccinated, although the effectiveness of the vaccine may be compromised because of the treatment-induced

immunosuppression (Ueno et al., 2005; Horn et al., 2009).

Also, apart from the emergence of HCV infection in IBD patients, the reverse can also happen: the emergence of IBD in patients with HCV infection; in such a case, it is generally thought that there was a latent and pre-existing IBD type (Khalil et al., 2005).

Cytomegalovirus (CMV)

Cytomegalovirus (CMV) is an opportunistic infection that may emerge in IBD patients under treatment with immunosuppressive agents. Most of primary CMV infections are asymptomatic, while even if the virus still exists latently after the infection, it is rarely found in IBD patients, usually in countries with low living standards. CMV colitis may emerge at the acute phase of CD or UC, and in case of a serious CMV infection, the treatment with immunosuppressive agents should be put to a halt and begin treatment for the viral infection (Garrido et al., 2013; Park et al., 2017).

IBD patients have also the risk of developing symptoms (lymphoma) due to EBV (Epstein-Barr virus) because of the immunosuppression. In most cases of EBV infection no antiviral treatment is required, whereas treatment with acyclovir is of low effectiveness (Nissen et al., 2015).

Clostridium Difficile Infection

The frequency of Clostridium difficile infection seems to be rising and it leads to an aggravated clinical picture, higher resistance to kinolones and increased mortality. The gravity of the clinical appearance and the risk of relapse depend on the patient's defensive capabilities. The risk of relapse is high and may occur repetitively. The use of immunosuppressive and not biological agents has been correlated to Clostridium difficile infections in IBD patients.

The majority of the persons carrying Clostridium difficile are asymptomatic carriers. Between healthy adults, the rates of Clostridium difficile circulation are 4 to 8%. In IBD patients, because Clostridium difficile infection or CMV infection entail high risk for serious complications, thorough examination for infections even at the early stages is highly suggested, along with proper treatment and cautious use of antibiotics in order to avoid the risk of resistance (Ananthakrishnan et al., 2011; Binion 2016).

Tuberculosis(TB)

As literature suggests, IBD patients have an increased risk for developing tuberculosis, even more so if they receive corticosteroids and/or are smokers (Keane et al., 2001; Danese et al., 2004). There have been reported cases of active TB in patients under treatment with Remicade. The main risk factors for developing TB included anti-TNF therapy, immunosuppression and hospitalization. In most of the cases, TB was extrapulmonary either localized or not. Before starting treatment with remicade, all patients should be assessed for active and latent TB. If active TB is diagnosed, treatment with Remicade should be cancelled. Also, use of anti-TB treatment should be considered before treatment with Remicade in patients with a history of active or latent TB but unknown treatment. Patients should know that if they have signs or symptoms denoting TB (persistent coughing, weakness, weight loss, low fever) while they are under treatment with Remicade, they should seek medical attention (Ramos et al., 2018).

Conclusions

IBD patients make up a priori a population with suppressed/compromised immune system. Those patients should be closely monitored for infections, including TB, before, during and after treatment with infliximab. Caution is warranted when infliximab is used with patients with chronic infection or a history of recurring infections simultaneously with immunosuppressive treatment. Thorough lab and clinical monitoring of IBD patients in order to identify opportunistic infections, should take place even at the early stages and also before the initiation of immunosuppressive treatment. Constant monitoring combined with the patients' comprehensive information and training, will render the patients' most effective and objective therapeutic approach, achievable.

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