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Sana Asghar[a] Syeda Komal Fatima[b] Nida Javaid[c] Naiha Tahir[d]

A Literature Review of Inflammatory Bowel Disease (IBD): It's epidemiology, Genetics, Pathogenesis, Prevalence and Treatment

Abstract *Inflammatory bowel disease (IBD) consists of two major inflammatory problems, which includes ulcerative colitis and Crohn's disease. Both are inflammatory conditions of the alimentary canal, but ulcerative colitis mostly affects the rectum and colon, whereas Crohn's disease affects the small intestine, large intestine, oesophagus and anus. This article highlights the causes, major role of genetic factors, the epidemiology, clinical implications, and treatment options available to deal with IBD.*

Key Words: Inflammatory Bowel Disease (IBD), Crohn's Disease, Ulcerative Colitis, Treatment, Epidemiology.

Introduction

Environmental and genetic predisposition produce changes in the immune system, which leads to inflammation in the intestine, causing severe disease of IBD. It is classified as Crohn's disease and ulcerative colitis. In this paper, we will deal with clinical aspects, including treatment regimens. US physician Burril B Crohn described Crohn's disease, and the name was given after him. In 1859, British physician Sir Samuel Wilks described ulcerative colitis.

Diet

Ulcerative colitis particularly depends on dietary patterns. Individuals with good dietary patterns had a 79% less chance of ulcerative colitis. Gluten susceptibility is mostly seen in IBD and linked with producing rage. 23.6 and 27.3% of Crohn's disease and ulcerative colitis patients confirmed this analysis. major risk factors for IBD and its reoccurring is diet having more protein and sugar. (Dolan & Chang, 2016)

Microbiota

Due to microbial mutualism and defense system, changes in the intestinal microbial number may contribute to different inflammatory intestinal diseases. There is a 30–50 percent reduction of a variation of mutualistic bacteria, such as a lesser number of Firmicutes and Bacteroidetes are found in IBD individuals. Further evidence that shows the role of gut flora in IBD is that these patients receive antibiotics for 2-5 years, whereas unexposed individuals do not. Various environmental factors affect bacteria, such as concentrated milk fats or oral medications (Nell et al., 2010).

[a] Undergrad 8th Semester, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan. Email: syedasanaasghar@gmail.com *(Corresponding Author)*
[b] Pharm D Graduate, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
[c] Undergrad 8th Semester, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan
[d] Undergrad 8th Semester, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.

Breach of Intestinal Barrier

Less coherence of the intestinal epithelium serves as a major contagious component in IBD. The problem in the inborn defence system due to abnormal signaling given by immune receptors called toll-like receptors (TLRs)produce signals, causes inflammatory conditions as well as cancer because they activate molecules used by different pathogens. Harmful disruption in the intestinal flora produces an immune response that is not controlled which leads to the destruction of the intestinal lining. Rupture in intestinal epithelium increases irruption of microbiota that bring out further defense system responses. The causes of IBD are many, but these amplified immune responses to gut flora is a major culprit. (Salim & Söderholm, 2011)

Genetics

The genetic component of IBD has been discovered earlier. The factors that help in research includes twin and epidemiological studies, studies of ethnic groups and familial aggregation. In the past decade, due to the use of molecular genetics, the discovery of genetic factors contributing to disease becomes easy. (Duerr, 1996). In 2001 first gene linked to IBD was NOD2. More than 200 SNPs (single nucleotide polymorphisms) are commonly linked with risk factors to IBD. A huge genetic study was carried out in 2012, which shows more variety of genes than previous studies. The result shows that there is an alteration in enteral flora in such a way that it produces inflammation. Various studies show that variation in IBD-linked genes might changes the interactions with the microbiome, responsible for normal immunological actions. Most of studies identified that chances of colon and rectal cancer and IBD increases with microRNAs hyperexcitability. To determine therapeutic agents, an association used biopsy material from IBD patient and analyzed it through Single-cell RNA sequencing. (Loddo & Romano, 2015)

Clinical implications

Although ulcerated colitis is different from Crohn's disease but the two of them share the common clinical manifestations such as abdominal pain diarrhea rectal bleeding sweat internal cramps in pelvis region and weight loss. Whereas on the extra-intestinal surface anemia is the most prevailing complication. Not only this but diseases such as arthritis, pyoderma gangrenosum, primary sclerosing cholangitis and nonthyroidal illness syndrome have also been shown to be associated with IBD. In some cases, deep vein thrombosis and bronchiolitis obliterans organizing pneumonia have also been reported to be associated with these diseases. For the diagnostic purposes the inflammatory markers in stools are assessed and then colonoscopy with biopsy of pathological legends is carried out.

Epidemiology

Statistics have shown that in countries like Denmark, North America and United Kingdom the occurrence and prevalence of UC and CD are highest birth rates are beginning to stabilize in these countries whereas on the other hand in Asia and countries like Spain, Romania and Italy although the incidence rates are low but there is a continuous increase in these rates. Studies shows that in North America the occurrence of CD in Asian and Hispanic communities is lower as compared to the white or black African- Americans. The race and ethnic origin are proved to be important as factors determining the risk of IBD by a study which compares the ailments outside the GIT with the racial differences in disease locality.

The Jewish people are more vulnerable to the prevalence of CD than any of the other racial group with the aspect of genetic anticipation. UC is 3-5 times more prevalent in Jews and important pharmacological differences exist between is the Israeli Jews and the others. The migration to other geographic areas equals the prevalence and this change in prevalence has been seen in other races as well. (For example, Chinese people living in Hong Kong in comparison with mainland China). Additional environmental and lifestyle effects have also been suggested by studying the increasing occurrence and prevalence of IBD in developing countries.

Surgery

Both UC and CD are the chronic inflammatory diseases that cannot be cured by medically. Although

UC can be cured by proctocolectomy in most of the cases, but the extra-intestinal symptoms cannot be eliminated by this practice. The feces can be collected in a bag by an ileostomy or on the other hand, the permanent ileostomy can be prevented by creating a pouch by using the small intestine which will perform role of a rectum. However, complications such as occasional or chronic pouchitis can occur in about ¼ to ½ of the patients with these pouches.

CD cannot be cured by surgery, but in extreme cases such as colostomy, bowel resection, ileostomy or strictureplasty may require surgery to treat the associated complications. In CD surgery is used to remove the highly inflamed segments and connect the healthy regions of the intestine but unfortunately this process cannot cure the disease as it can reoccur in those healthy regions after surgery, usually at the site of surgery. (e.g, A patient is having CD and has had ileocecal anastomosis his Crohn's will always outburst near the resection site or in the other parts of the ascending colon.)

Medical Treatment

Medical therapies of IBD are specific for the patients. The selection of drug and its route of administration is based on many factors such as the patient's compliance, the type of disease, its severity and distribution. For example, the drug mesalazine is frequently used to treat UC rather than CD. Whereas immunosuppressants such as TNF inhibitors, methotrexate, azathioprine, 6-marcaptopurine or prednisone are used in severe IBD.

The once acceptable maintenance drugs, the steroids like the glucocorticoid Prednisone are used to prevent the exacerbation of IBD whereas the TNF inhibitors used as the biological therapy are more often used in patients with chronic or resistant CD.

The treatment starts with the administration of highly effective anti-inflammatory drug such as prednisone. After successful control of inflammation, the main treatment includes the drug which is used for the reduction or disappearance of the symptoms, such as mesalazine in UC. In case of further discomfort of patient, an immunosuppressive drug (e.g., azathioprine) may be used in combination with mesalazine as the next step. Patients with mild ileal CD are given controlled release budesonide.

Treatment

The pharmacological treatment employed currently is focused on the mitigation of symptoms but does not target the cure of actual mechanism causing the disease. Generally, pharmacotherapy of IBD includes drugs like aminosalicylates, corticosteroids and immunosuppressant agents depending on the type of therapy opted, for instance, corticosteroids are well-tolerated for short-term treatment while immunosuppressants are suitable for long-term. However, a novel approach focuses on treating the root-cause, the biochemical inflammation in the Gastrointestinal tract. This can be done via humanized monoclonal antibody formulations that targets the immune responses that sprout. The improved biotechnology coupled with second generation agents have manifested prosperous consequences.

The First line therapy for trivial to modest Ulcerative Colitis (UC) are aminosalicylates like Mesalamine while for maintaining remission, Sulfasalazine is the drug of choice. Although these are salicylates but their therapeutic influence emphases on impending sites like inhibition of inflammatory agents like Interleukin 6 (IL-6), Tumor Necrotic factor alpha (TNF-α) and NF-κB, blocking lipoxygenase pathway also, reducing oxidative stress.

Prednisolone or another member of the glucocorticoid family, Hydrocortisone are main players in the treatment of IBD. They can be given via different routes, alone or combined with other agents. Patients' response to Steroids divide them into 3 categories based on their perceived responses. These are: responsive, dependent or unresponsive. The regimen of steroids is decided according to the response attained (Aberra et al 2003).

For IBD, Azathioprine and Mercaptopurine have been the leading immunosuppressant choice. They have proven to be better than corticosteroid therapy in regard to safety and tolerability. Methoterexate has also shown favorable results in patients.

Intravenous Cyclosporine shows promising results in severe UC and saves from emergency colectomy.

Monoclonal antibodies also known as "biological response modifiers" are very target-oriented drugs that mitigate inflammatory agents like TNF-α in case of Crohn's disease. Infliximab is the key participant here and has exhibited encouraging responses.

Symptoms of IBD can be alleviated using agents like antibiotics, supportive treatment and salts like those of bismuth and sodium cromoglycate, fish oils and thalidomide – only in limited cases. Herbal therapies can also play an accessory role along with medication. These remedies include probiotics, Oral aloe vera gel, diet control and folic acid.

Therapy with Diet and Nutritional Requirements

Ulcerative colitis and Crohn's disease both are the contributing factors of IBD. Insufficient nutrition has a major role in the development of Inflammatory Bowl Diseases. The basic characterization of IBD include diarrhea, Malabsorption, and loss of blood from GI (Wędrychowicz, 2016). Along with these, body becomes deficient of several vitamins, fatty acids that are essential for body and minerals like Zinc, Magnesium and Selenium.

- The deficiency of minerals can be coped with replacement therapy.
- The symptoms of IBD can be well managed and relieved with the help of special diets like specific carbohydrate diet and by taking supplements like psyllium supplementation where a mixture of soluble and insoluble fibers is taken, respectively.
- The levels of iron that are reduced due to anemia in both ulcer and Crohn's disease condition is then improved with the help of this nutritional therapy which aims to raise the level of hemoglobin in the patient with IBD.
- Both Parenteral and Eternal nutritional therapies are used but Eternal nutrition therapy is used specifically to prevent the further progression and re-occurrence of Crohn's disease because sometimes it happens that the symptoms disappear temporarily and then re-appeared suddenly so it is should be prevented. This is used as first line therapy in case of CD (Alhagamhmad et al., 2012).

  In this way, this kind of therapy helps to improve the immune system, reduce the inflammatory actions, and brings back the intestinal mucosal lining to its nearly original condition so blood lost can be prevented.

Microbiome

According to some old evidence, it is revealed that some infectious diseases also contribute to IBD, so in such cases patient are getting treatment with antibiotics e.g., rifaximin.

The usefulness of antibiotic is merely limited to Crohn's disease and to some extent its also working in ulcerative colitis.

- Another option for the treatment of IBD is Fecal microbiota transplant, a new advancement that is quite safe but still need some trials to make sure that it is beneficial completely (Gevers et al., 2017).

Alternative treatments/therapies

Alternative therapies (Fernández et al., 2012) used during UC and CD include:

- Herbal therapy with the help of Plantago ovata
- UC maintenance therapy using Curcumin.
- Mind/Body therapy & self-intervention in case of UC (ulcerative colitis)
- Use of wormwood in case of CD (Crohn's disease)
- Acupuncture in UC and CD

Newer and Novel Approaches

Stem cell therapy is under consideration to be used for the treatment of IBD safely but due to immense challenges including the cost of this approach is basically the reason that its use is limited clinically.

Diagnosis of IBD

- The initial inspection of IBD is done with the help of Fecal calprotectin (Büller, 1997) while

diagnosis is done with the help of biopsy where tissue culture from colon is being examined.

- Liver function tests are also performed because level of proteins/enzymes are also elevated in this case which leads to hepatotoxicity and fatty liver.

Other tests including blood tests, stool examination, endoscopy, and imaging study also help to find out other factors responsible and confirm the diagnosis of IBD (Bernstein et al., 2010).

Some similar diseases may also produce the same situations so IBD must be differentiated with the help of the following tests discussed earlier so the disease can be diagnosed and treated properly.

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