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Yonina Wallerstein

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Yonina Wallerstein is currently attending the Touro University Physician's Assistant Program at Central Islip, NY

Abstract

Objective: This paper discusses the research available regarding risk factors of Crohn's disease. Risk factors are analyzed to determine which are the most likely to cause pathogenesis. Discussion includes a definition of the disease, including new ways to diagnose and treat it. Prevalence amongst different populations is reviewed to consider a broad variety of environmental and genetic factors. Risk factors and research of affected populations lead to the study of the microbiome and how that must be further studied to broaden understanding and treatment options.

A Definition Disease and an Overview of Risk Factors and Treatments of Crohn's

Crohn's disease falls under the category of an IBD or Irritable Bowel Disease, which is diagnosed based on intestinal inflammation. "Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract with symptoms evolving in a relapsing and remitting manner" (Torres, et. al. 2017). The journal article defines Crohn's disease as an inflammatory disease of the gastrointestinal tract. Inflammation can occur anywhere along the tract and can affect multiple layers of the tissue (Kalla, et. al. 2014). The inflammation does not always remain exclusively in its original area. Crohn's disease does not have any known cure, but it does have many treatments that can effectively control the condition and heal the inflammation. This period of healing can last a long time and is referred to as remission. A return of symptoms is called a flare-up. Treatments for Crohn's disease include pharmaceutical drugs, surgery, and specialized diets. Risk factors are varied; however, studies have suggested combinations of genetic factors, environmental factors, antibiotic usage, microbial causes, and family background influence. Although there are a multitude of risk factors, research does suggest that microbial dysbiosis may be the most significant.

Methods

Peer-reviewed journal articles accessed through the Touro online library and the ProQuest database were used to gather data for this article. Other research websites and various papers to gain a comprehensive understanding of the subject matter.

Results

A deeper understanding of Crohn's disease is vital to understanding the experiments conducted to determine possible risk factors and treatments. It is also needed to understand the reasoning behind the attempted treatments and their level of success. Crohn's disease is a complex disease because of its spectrum of severity and affected areas. It is an idiopathic autoimmune disorder and is classified through a biopsy of the tissue. Gastrointestinal tissue affected by Crohn's will have a "cobblestone effect", discontinuous inflammation or ulceration (otherwise known as skip lesions), and rectal sparing (Kalla, et. al. 2014). The "cobblestone effect" refers to the affected tissue's fissuring and serpiginous ulcerations (Caio, et. al. 2021). Crohn's disease is classified by three different phenotypes; inflammatory, stenosing, and penetrating (Caio, et. al. 2021). It is also classified using the Montreal classification, which classifies based on the affected area: L1- Ileal, L2- Colonic, L3- Ileocolonic, L4- Upper Gastrointestinal, P- Perianal. Each of these areas presents with different symptoms (Kalla, et. al. 2014).

Studies of the suggested pathogenetic mechanisms of Crohn's Disease reveal that there isno simple explanation. As many as 170 different risk factors have been identified in association with Crohn's disease (Rogler and Hausmann, 2019). Study results tended to be inconclusive, and the general consensus among researchers is that more data must be gathered if we wish to understand this complex disorder.

Epidemiological studies have indicated that there are environmental risk factors for Crohn's disease (Genin, et. al. 2020). Crohn's disease has long been considered a disease in Western countries. The rates of Crohn's disease are much higher in Western countries such as the United Kingdom, France, and the USA. However, westernizing countries have seen a rise in the prevalence of Crohn's disease as well, suggesting a possible connection between a western lifestyle and this disease (Aniwan, et. al. 2017). Western countries experienced an extreme rise in cases during its surge of socioeconomic advancement during the latter half of the 1900's. The swift rise of incidence in South America, Eastern Europe, Asia, and Africa correlates to the socioeconomic advancement that is taking place in those countries now (Ng, et. al. 2017).

An epidemiological study in France traced diagnoses of Crohn's disease from 2007-2014 to find any statistically significant areas with the disease. The study found that there were sixteen spatial clusters (specific localized areas with higher prevalence) in France where the prevalence of Crohn's disease was significantly higher. Northern France contained most of the clusters, and also included a super-cluster in the Northern/Northeastern border that accounts for 35% of the cases in the study (Genin, et. al. 2020). The researchers concluded that the areas of higher prevalence were also more urbanized and underserved compared to other areas of France. This conclusion matched earlier studies in France that found that Northern France had a much greater prevalence of

Crohn's disease and that areas that were economically disadvantaged had a higher rate as well
(Nerich, et. al, 2006).

One obvious risk factor is smoking. It has been strongly correlated with relapses (an increased risk by 65%), and stopping can be as effective as immunomodulatory therapy (Kalla, et. al. 2014). Studies have demonstrated that smoking reduces the effect of treatments while the patients are undergoing them. A group of researchers analyzed eighteen observational studies and five randomized control trials. They found that smokers (defined as having at least five cigarettes a day for five months) treated with biologics were less likely to respond when compared to non- smokers (Lee, et. al. 2021). Biologics are anti-TNF drugs that interfere with inflammatory responses, and are a preferred treatment for Crohn's disease. Lee's study also found that smoking prevented clinical remission, although this was only seen in the observational studies and not in the randomized clinical trials. The difference between Lee's analysis and Kalla's analysis can possibly be explained by Lee's later publishing date (2021) versus Kalla's (2014). The later publishing date gave Lee's study more data to analyze.

Another study that analyzed the effects of smoking on Crohn's disease also found that smoking had no correlation with disease severity. However, the study did found there was a difference in the gut bacteria between smokers and non-smokers. Using the Kruskal-Wallis test, the study found that the Peptostreptococcaceae genus of bacteria was higher in smokers with Crohn's disease, and the Eggerthella lenta genus was higher in non- smokers (Pascal, et. al. 2017). Further studies could analyze the effects of these bacteria on the course of Crohn's disease.
Others have studied obesity as a risk factor for IBD. The study differentiated between Ulcerative Colitis and Crohn's disease. A large randomized group of IBD patients were selected for the study. Test subjects answered lifestyle questions such as smoking and eating habits. Patients' BMI were also collected at the beginning of the study. Although obesity did not emerge as a statistically significant risk factor for all ages, it did emerge as statistically significant when adjusted for the forty- five years and older bracket. However, this finding was unique to Crohn's disease. Ulcerative colitis had no correlation to obesity in the experiment. (Mendall, et. al., 2011).

Genetic factors have been examined as well. As of 2018, more than 170 genetic risk factors were associated with Crohn's disease and at least seventy different chromosomal loci were identified (Kupka, et. al. 2018). Many other inflammatory diseases, such as ankylosing spondylitis, psoriasis, diabetes, and lupus share the same genetic risk factors (Rogler and Hausmann, 2019). In 2001, research groups independently released studies that proved the connection between the NOD2 gene (also known as the CARD15 gene) and Crohn's disease (Cho 2008, Kupka, et. al. 2018; Rogler and Hausmann, 2019). This discovery opened the door for research into genetic factors of Crohn's disease (Rogler and Hausmann, 2019). Further research in the NOD2/CARD15 gene showed that there are multiple mutations that are all associated with Crohn's disease (Kupka, et. al. 2018).

NOD2/CARD 15 has three different mutations identified as risk factors for Crohn's disease. These mutations are classified as R702W, G908R, and 3020insC and account for at least 81% of NOD2/CARD15 mutations in patients with Crohn's disease. An analysis of multiple studies has determined that a heterozygous carrier of the NOD2/CARD15 mutation has a 2-4 higher risk of developing Crohn's disease and a homozygous carrier is seventeen times more likely to develop Crohn's disease (Kupka, et. al. 2018). These studies have been replicated consistently in populations with European ancestry but not in populations of African or Asian descent (Cho, 2008). This gene codes for a protein that is an innate immune receptor for a part of the bacterial cell wall. When the NOD2/CARD15 gene is mutated, the body's ability to recognize the bacterial cell wall is compromised (Rogler and Hausmann, 2019).

Multiple studies confirmed that Crohn's disease runs in families, with Ashkenazi Jews, (ancestry in Central and Eastern Europe) used as a model for Crohn's disease research. Ashkenazi Jewry has the highest percentage worldwide of IBD diagnoses with a rate that can be 2-4.3-fold greater than the rest of its epidemiological population (Mayberry, et.al. 1986). Although Crohn's disease risk factor genes have been identified in Ashkenazi Jewish patients, they do not account for the much greater rate of diagnosed patients (Hui, 2014; Sugimura, et. al. 2003). The three NORD2/CARD15 mutations that have been identified in Ashkenazi Jews have also been identified in 30-40% of all Crohn's disease patients. Therefore, they do not account for the greater prevalence of Crohn's disease in Ashkenazi Jewry. A team of researchers studied the genetics of sixty-four Ashkenazi Jewish families and 147 non-Jewish white families. They identified a new haplotype of the NORD2/CARD 15 gene at the IBD1 locus that was unique to the Ashkenazi Jewish patients. This led to a hypothesis that it is rather this gene that contributes to the higher rate of Crohn's disease in Ashkenazi Jews and gives its Ashkenazi Jewish carriers a predisposition to Crohn's disease (Sugimura, et. al. 2003).

A team of researchers in Israel studied a group of Jewish

Crohn's disease patients with perianal disease. These researchers found that none of their patients with perianal disease had any of the classic Crohn's disease genetic markers. Although the NORD2/CARD15 gene is common in Jewish Crohn's disease patients, the patients in the study did not have this genetic risk factor. After extensive genotyping and phenotyping, the researchers established that there was no known genetic risk factor for perianal Crohn's disease in their study. However, they did find that being a Sephardic Jew, (ancestry from the Iberian Peninsula), was a statistically significant risk factor for developing perianal disease as a Crohn's disease patient (Karban, et. al. 2007). This is interesting because studies on Jewish patients with Crohn's disease have only found being an Ashkenazi Jew as a risk factor, while this study found being a Sephardic Jew as a risk factor as well.

The NOD2/CARD15 discovery opened the door to the next part of Crohn's disease research-the connection between Crohn's disease and intestinal bacteria. Researchers found that IBD was associated with immune dysfunction connected to intestinal flora (Rogler and Hausmann, 2019). Human bodies have large amounts of intestinal flora that live in a commensal environment in the gut. However, some bacterial invaders need to be attacked by the immune system. The immune system's job is to differentiate between the two and only kill the harmful bacteria. There is strong evidence that a major IBD cause is when the immune system cannot differentiate between the good and bad bacteria in the gut. One indication that there is a connection between IBD and intestinal bacteria is that the areas with the highest concentration of bacteria are the areas with the highest prevalence of IBD (Cho, 2008).

Multiple studies have been done to analyze the connection between gut bacteria and Irritable Bowel Disease. A study done by researchers in Spain and Belgium found that Crohn's disease had clear parameters for gut dysbiosis and Ulcerative colitis did not. This study was built on previous studies which found that patients with Crohn's disease had decreased bacteria from the order Clostridiales and increased bacteria from the order Enterobacteriales as compared to healthy patients (Pascal, et. al. 2017). Their study used 669 new patients and 1376 patients that already had their gut bacteria genetically sequenced, creating an unusually large study over four countries: Spain, Belgium, Germany, and the United Kingdom.

Bacteria were studied in the experiment through fecal samples that underwent genetic sequencing for different bacteria. Patients enrolled in the study provided samples at 3-month intervals over one year and a sample if they suffered a flare-up. First degree relatives of the patients were also included and provided samples as well. Results of the study showed that the samples from patients with Crohn's disease showed the highest rate of bacterial instability over time as compared with their healthy relatives and those with Ulcerative colitis. This was in contrast with patients with Ulcerative colitis, whose microbiomes were more stable than their healthy relatives (Pascal, et. al. 2017).

The human microbiome is mostly made up of anaerobic bacteria from the phyla Firmicutes and Bacteriodetes (Oberc and Coombes, 2015). An early study on the connection between the microbiome and Crohn's disease found a decrease in the Clostridium leptum group (Manichanh, et. al. 2006). This group is a butyrate producer, which is a short chain fatty acid (SCFA). SCFA are an energy source for the intestinal epithelium. Butyrate also is known to lower inflammatory mRNA and acidify the intestinal lumen, which scientists consider a possible blocker for pathogens like Salmonella and E. coli (Oberc and Coombes, 2015). One study found that microbes in patients with IBD lack proper pathways for amino acid synthesis and have increased amino acid uptake (Gaboriau-Routhiau, et. al. 2009).

Analysis of the microbiome in patients with Crohn's disease has been complicated by scientists' inability to determine what treatments the Crohn's disease patients had already undergone. One study tried to remedy possible exposure to risk factors and treatments by studying pediatric patients who had not undergone any treatment for Crohn's disease (known as treatment naïve) (Gevers, et. al. 2014). This study also analyzed bacteria in tissue samples instead of stool samples for a more accurate portrayal of the microbiome. It compared confirmed pediatric treatment naïve patients with control pediatric patients that had non-inflammatory abdominal symptoms. Results of the study showed a decrease in the variety of the microbiome in patients with Crohn's disease and changes in the amounts of certain taxa of bacteria. Specifically, taxa Pasteurellaceae (Haemophilus sp.), Veillonellaceae, Neisseriaceae, and Fusobacteriaceae were all new discoveries that positively correlated with Crohn's disease. Fusobacterium, from the family Fusobacteriaceae, had been previously suggested as a biomarker for Crohn's disease (Strauss, et. al. 2011). When these results were compared with stool samples collected from the same patients, many of the bacteria were missing from the stool. These results suggest that Crohn's disease is connected with microbiome dysbiosis, and can be diagnosed through a tissue biopsy of the affected area (Gevers, et. al. 2014)

One hypothesis for a cause of the microbiome dysbiosis is antibiotic usage. Antibiotics have been found to reduce the variety of bacteria in the microbiome and to

shift the microbiome entirely (Jakobsson, et. al. 2010). In the study on pediatric patients with treatment naïve Crohn's disease, a small subset of subjects was on antibiotics during their tissue biopsy. The dysbiosis was more extreme in these patients, with a 10-fold increase in the Fusobacteriaceae in the ileum and the Enterobacteriaceae in the rectum. The Veillonellaceae were decreased in the stool and rectum while the Pasteurellaceae were decreased in the ileum. This led researchers to hypothesize that antibiotics have a strong effect on the microbiome and can possibly be connected to the development of the microbiome dysbiosis associated with Crohn's disease (Gevers, et. al. 2014).

Discussion

Crohn's disease remains an elusive disease. Scientists are still struggling to understand what triggers its development. However, they have found promising leads in understanding its connection to socioeconomic advancement, westernization, genetic factors, and microbiome dysbiosis. Microbiome dysbiosis, in particular, seems to be a particularly intriguing path towards simpler diagnoses and treatments. If we can crack the code of the microbiome in the gut and its connection to Crohn's disease, there's a possibility of understanding what is going wrong in the GI tract in patients with Crohn's disease.

There are still many areas of research waiting to be studied. Crohn's disease is still lumped together with Ulcerative Colitis, although all research points toward there being a big difference between the two. The mind-body connection involved in Crohn's disease has also been severely understudied. There is also a lack of knowledge in the general public about microbiome dysbiosis and its connection to Crohn's disease. It would seem that the microbiome has to be understood to develop accurate diagnosis and treatment. More information about the microbes that live in every person needs to be available to the general public, especially to people living with Crohn's disease.

Conclusion

Through researching and understanding the risk factors of Crohn's disease, one can determine possible triggers that are involved in the development of Crohn's disease. Although research points towards a more complex explanation rather than one simple cause, it also demonstrates that we are closer to understanding Crohn's disease. Microbiome dysbiosis and socioeconomic factors both have strong potential to be the focus of future research on Crohn's disease. However, Crohn's disease research is always evolving, with areas clearly needing cutting edge techniques. Advances in microbiology and genetic sequencing and analyses will continue to support better understanding and treatments, leading to better outcomes for sufferers of this complex disease.

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