The Corinthian

Volume 13 Article 4

2012

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Introduction

Crohn's disease (CD) is defined by chronic inflammation of an isolated portion of the gastrointestinal track (Longo & Fauci, 2010). Frequently, the site of inflammation is the proximal portion of the colon, or less commonly, the terminal ileum (Schilling-McCann, 2008). Other names for the disease frequently reported in medical literature and research include regional enteritis and granulomatous colitis. The specific etiology of CD is idiopathic but there are several widely accepted theories.

Two of these theories are predominantly acknowledged throughout the medical community. According to the National Digestive Diseases Information Clearing House (NDDICH), a chronic autoimmune reaction to bacteria and specific nutrient ingestion is the most popular medical theory used to explain the condition (NDDICH, 2010). Tersigni and Prantera (2010) address another popular explanation, suggesting the etiology of inflammatory bowel diseases is a genetic predisposition to dysregulation of the gastrointestinal system.

Various organizations and researchers have attempted to estimate the incidence and overall prevalence of CD resulting in a range of epidemiological estimates. In recent years, both the incidence and prevalence of CD have increased (Hyman, 2009; Loftus, Schoenfeld, & Sandborn, 2002; Neal, 2009). One investigation reported the incidence as rapidly increasing between the late 1950s and early 1970s and thereafter stabilizing at roughly seven cases/100,000 person-years (Loftus, Schoenfeld, & Sandborn, 2002). However, a recent report published by Digestive Disease Weekly cites a dramatic increase of 20.7% in the incidence during the last decade in European countries (Neal, 2009). Although there have not been extensive epidemiological studies in North America, many experts have cited it as a growing problem, linking it to many other disease of increasing incidence (Hyman, 2009).

According to the Crohn's and Colitis Foundation of America (CCFA), the combined prevalence of CD and ulcerative colitis (a closely related disease) is currently 1.4 million in the U.S. (CCFA, 2009). The pharmaceutical company Nexcare Inc. (2003) estimates the prevalence of CD at 183.82/100,000 individuals, or 1 in every 544 citizens that live in the U.S. A national survey throughout random communities for Irritable Bowel Syndrome (IBS; almost an even split between ulcerative colitis and Crohn's) reported a standardized prevalence rate of 8.1% for the population (Wilson, Roberts, Roalfe, Bridge, &

Singh, 2004). Overall, the estimates of CD may reflect the various sampling and reporting techniques used in the preceding epidemiological estimations.

Risk Factors

There is an abundance of literature addressing the possible risk factors that are strongly associated with CD (Braat, Peppelenbosch, & Hommes, 2006; Chitkara, van Tilburg, Blois-Martin, andWhitehead, 2008). While there is a mass of these potential variables, several have been sighted within the medical literature and appear to be the most commonly identified, including smoking, use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), and medication used for cystic acne (Isotretinoin).

There is a general consensus among gastroenterologists that smoking is the most important modifiable risk factor for those at risk for developing CD (Katschinski, Logan, Edmond, & Langman, 1988). It has been shown that this behavior is not only detrimental to intestinal health through the inhalation of over 4,000 chemicals, but also increases the risk of colorectal surgery (Laghi et al., 2005). Several epidemiological studies have demonstrated that smoking cessation increases the likelihood of remission (Cosnes, Beaugerie, Carbonnel, & Gendre, 2001; Cosnes et al., 1999; Johnson, Cosnes, & Mansfield, 2005) with an even sharper increase in improvement after surgery (Reese et al., 2008). A study conducted by Somerville and colleagues (1984) indicated that although patients that smoked suffered from more severe symptoms, improvement and even remission was possible with smoking cessation.

According to Evans and colleagues (1997), there is also a strong association between hospital admittance of patients with CD and the use of NSAIDS. Additional studies have indicated NSAIDS are not the only drugs that are documented to increase one's risk of developing CD. Isotretinoin (Accutane©), a now frequently prescribed drug used to treat acne in teenagers and young adults has been associated with the diagnosis of CD and Irritable Bowel Syndrome (Crockett, Portal, Martin, Sandler, & Kappelman, 2010; Shale, Kaplan, Panaccione, & Ghosh, 2009). Many teenagers that were diagnosed with CD were shown to have taken Isotretinoin in recent years (Margolis, Fanelli, Hoffstad, & Lewis, 2010). Although a direct biochemical or physiological link has not yet been established, the relationship between CD and these medications is currently being investigated (Reddy, Siegel, Sands, & Kane, 2006).

While tobacco and certain pharmaceutical drugs have been targeted as strong risk factors for the disease, additional genetic, cultural, and behavioral factors may also play a role. Age, ethnicity, and family history have all been identified as contributors to a individual's risk (Gearry, Richardson, Frampton,

Dodgshun, & Barclay, 2010). Findings from a study conducted by Polito and colleagues (1996) revealed that over 80% of those diagnosed with CD were 20 years old or younger; and 1 out of 5 of those diagnosed had a relative that is affected by the condition. While a causal relationship between CD and age has not been identified, further epidemiological studies are needed to assess their potential association.

Symptoms and Diagnostic Methods

Although CD can present in a variety of manners, the majority of cases exhibit symptoms of diarrhea, abdominal pain and cramping, blood in the fecal matter, ulcers, reduced appetite, and weight loss (Mayo Clinic, 2011). Less common symptoms observed include fever, fatigue, arthritis, inflammation of the eye, skin disorders, inflammation of the liver or bile ducts, and delayed growth or abnormal sexual development (Mayo Clinic, 2011). Individuals should seek medical attention and visit their primary care physician when they experience prolonged abdominal pain, observe blood in the stool following bowel movements, diarrhea lasting more than two days and is unresponsive to over-the-counter medications, or unexplained fever lasting more than 24 hours (Mayo Clinic, 2011).

Most patients who have CD are unaware of it until a diagnosis has been made. Frequently, they will make an appointment with their primary care providers to discuss commonly reported digestive issues. If the provider renders the case as serious, the patient will be referred to a gastroenterologist. Only then, will endoscopy and colonoscopy be preformed in order to collect biopsy samples of the gastrointestinal tract. In most cases, they are taken from the colon, but they may be collected elsewhere, depending on where the physician believes the atypical cells are located in the body. The analysis of these samples is by far the most definitive way to diagnose the condition.

According to Chandrasoma (1999):

> Histologic examination of endoscopic biopsy samples is the best method for establishing the diagnosis of IBD in a patient with symptoms of colitis. Features in the biopsy specimen permit accurate differentiation of acute self-limited colitis and IBD in the majority of cases (p.309).

Chandrasoma (1999) reported that once biopsy samples have been collected, every effort is made by the pathologist to categorize the results as either CD or ulcerative colitis.

Susceptible Causes

The pathological components of CD have been intensely researched and a multitude of findings have been published on the subject. In spite of this, no definitive etiological process has been identified. There is some evidence that *Escherichia coli* may play a key role (Peeters, Joossens, & Vermeire, 2001), based upon a deficiency of defensins caused by a theoretical dysfunction of the NOD2/CARD15 gene (Fellermann, Wehkamp, Herrlinger, & Stange, 2003). This is supported by the presence of *E. coli* found within the ileal mucosa of CD patients (Darfeuille-Michaud et al., 2004). Furthermore, research conducted by Sasaki and colleagues (2007) documented growing strains of invasive *E. coli* cultures obtained from CD patients. During their investigation, all bacterial samples taken from CD patients were identified as *E.coli* regardless of the disease activity in a variety of tissues.

A form of fungus that is conjectured as a cause of CD is *Candida albicans* (Nahas, 2011). A study published in the *American Journal of Gastroenterology* by Standaert-Vitse and colleagues (2009) reported a correlation between high levels of *C. albicans* and CD in 129 patients with a median age of 45 years. In addition, previous research has found that over half of patients who suffer from CD also exhibit higher levels of anti-S. cerevisiae antibodies (ASCAs; Peeters, Joossens, & Vermeire, 2001; Quinton, Sendid, & Reumaux, 1998). Standaert-Vitse and colleagues (2009) suggested that these abnormally high levels of ASCAs may be caused by *C. albicans*.

Treatment

While physicians from various medical philosophies agree upon the diagnosis criteria for CD, there is no consensus among practitioners regarding proper course of treatment; and divisions exist within both conventional and alternative approaches. If the pathogenesis is severe, many allopathic physicians recommend antibiotics for treatment of the abscesses and inflammation (Bressler, & Sands, 2006; Greenbloom, Steinhart, Greenberg, 1998). Others question this theory as antibiotics are known to irritate the gastrointestinal tract as well as diminish the number of colonies of bacteria that have been shown to be the basis of the human immune system (Levy, 2000). However, balance of gastrointestinal flora may be reestablished through supplementation of probiotics (Johnston, Supina, & Vohra, 2006). When the disease process appears to be stable, allopathic medicine suggests the prescription of either corticosteroids such as Budesonide (Entocort EC) or a form of mild chemotherapy such as Infliximab (Remicaid©; Benchimol, Seow, Otley, & Steinhart, 2009; Sands et al., 2004).

Conventional Treatment

The pathophysiological details of CD are not clear nor is there a definitive course of treatment leading to certain life-long remission. Due to this difficulty, the conventional treatment for CD is highly debated. Therefore allopathic practitioners utilize a variety of pharmacological therapeutic modalities, all of which seek remission in the patient for as long as possible (Lichtenstein, Hanauer, & Sandborn, 2009).

Sellin and Pasrichia (2006) state:

> Medical therapy for Irritable Bowel Disease is problematic. Because no unique abnormality has been identified, current therapy seeks to dampen the generalized inflammatory response; however no agent can readily accomplish this, and the response of an individual patient to a given medicine may be limited and unpredictable (p. 1009).

Following conventional allopathic medical philosophy, treatment is selected based upon the severity of the disease process at the time it is to be rendered (Akobeng, 2008; Clarke & Regueiro, 2009; Colombel, et al., 2010; Schwartz, Pemberton, & Sandborn, 2001). Patients experiencing mild symptoms are advised to take over-the-counter medications to manage symptoms, such as Loperamide for diarrhea, milk of magnesia for constipation, and iron supplements to treat deficiency caused by excessive bowel movements (Hanauer, 2008). For patients experiencing mild to moderate symptoms, there are several classes of pharmaceuticals that can be utilized to reduce the intensity of symptoms and/or promote induction of remission (Akobeng, 2008). Though there is much debate on the proper course of treatment, physicians typically select a medication based on the intensity of the symptoms. Commonly prescribed drug classifications include: aminosalicylates, antibiotics, corticosteroids, immunosuppressants, biologics, rifaximin, tacrolimus (Sellin & Pasricha, 2006).

For those that experience mild to moderate symptoms, one of several medications may be prescribed. Mesalamine (5-aminosalicylic acid, 5-ASA) and sulfasalazine is generally used as the "first line of defense" for CD (Sellin & Pasricha, 2006). However, Sulfasalazine has not been shown to be efficacious in the maintenance of remission and more recently other 5-ASA preparations have been prescribed (Sellin & Pasricha, 2006). Two of these new preparations, Pentasa (mesalamine) and Asacol (mesalamine) have become popular in the gastrointestinal community due to their rate of admittance into remission (Lim & Hanauer, 2010). There is no clear benefit of continuing this type of therapy once patients enter remission. This causes their use as a maintenance drug to be controversial (Sellin & Pasricha, 2006).

Glucocorticoids and steroids may also be used as treatment for mild to moderate symptoms, depending on whether the case of CD is steroid-responsive, steroid-dependent, or steroid-unresponsive (Lemann et al., 2006). In ideal cases, steroid-responsive patients will show improvement within 1-2 weeks of treatment and remain in remission. Future steroid use is tapered off and eventually discontinued (Sellin & Pasricha, 2006). Patients classified as "steroid-dependent" respond to initial treatment administration yet their symptoms begin to reoccur after the treatment is tapered off or stopped. Approximately 40% of patients are steroid-responsive, 30% to 40% have only a partial response or become steroid-dependent, and 15% to 20% do not respond to steroid therapy at all (Sellin & Pasricha, 2006).

Thiopurine derivatives are prescribed for patients who are experiencing moderate to severe symptoms of CD and are either steroid dependent or steroid resistant (Sellin & Pasricha, 2006). Mercaptopurine (6-MP), known on the market as Purinethol®, and Azathioprine, known commonly as Immuran are two of the most commonly used thiopurines for CD (Sellin & Pasricha, 2006). Both have been shown to be successful in inducing remission but are sometimes viewed as non-viable options due to the uncomfortable side effects experienced in some patients, such as nausea, vomiting, diarrhea, and loss of appetite. In addition, thiopurines may take several weeks or months to induce therapeutic effects in patients making them the less desirable choice for acute symptoms or flare-ups (Sellin & Pasricha, 2006).

Methotrexate, originally developed as an anti-cancer drug, was later recognized as an effective treatment for psoriasis and rheumatoid arthritis (Sellin & Pasricha, 2006). Since the 1990s, Methotrexate has also been shown to be useful in the treatment of CD, with current research still supporting this data (Chande, Abdelgadir, & Gregor, 2011; Feagan et al., 1995). It is also typically reserved for patients who are steroid-resistant or steroid-dependent (Sellin & Pasricha, 2006). Known for its ability to induce and maintain remission, it can be a desirable choice due to a patients' quick response to its therapeutic properties (Alfadhli, McDonald, & Feagan, 2005).

A relatively new form of biologics, anti-tumor necrosis factor alpha (TNF- α) therapy, has become an extremely popular treatment option for CD in the last decade. TNF- α binds with a chimeric immunoglobin causing it to become neutralized (Panés et al., 2007). There are many different cytokines generated in the intestine of a patient suffering from CD but there is rationale suggesting TNF- α is one of the principal cytokines mediating the T_H1 immune response, a primary immunological characteristic of the disease (Sellin & Pasricha, 2006).

Infliximab (Remicaid©) is a relatively new pharmaceutical, and has been established as beneficial for CD patients. Two-thirds of patients with

moderate to severe cases indicate a decrease in the frequency of acute flares when treated with Infliximab (Sellin & Pasricha, 2006). Though its use as a long-term treatment has yet to be thoroughly ascertained, current research supports the medication's efficacy in preventing the recurrence of fistulas and maintaining remission (Present et al., 1999; Schröder, Blumenstein, Schulte-Bockholt, & Stein, 2004). While it may seem like a panacea, there is also data that causes practitioners to heed caution due to adverse side effects, both acute and sub-acute. Some of the adverse effects include fever, chills, urticarial, anaphylaxis, and serum sickness (Sellin & Pasricha, 2006). Therapy with Infliximab has also been shown to increase the incidence of respiratory infections, reactivity of tuberculosis, and complications in patients with congestive heart failure (Sellin & Pasricha, 2006). In addition, it shares an association of increased incidence of non-Hodgkin's lymphoma, as is the case with most immunosuppressants (Bebb & Logan, 2001; Lakatos & Miheller, 2010). More research is needed to fully understand the beneficial effects of medications used to reduce TNA-α. For example, *Etaneracept* have demonstrated limited efficacy. Furthermore, additional research is needed to explore potential methods to limit the side effects of medications that have been identified as beneficial for CD patients.

Antibiotics may be used to treat CD for a number of reasons, including prophylaxis for recurrence in postoperative CD, treatment for a specific complication of CD, or adjunctive treatment along with other medications for active CD (Feller et al., 2010). The most frequently used antibiotics are *Metronidazole, Ciprofloxacin,* and *Clarithromycin* (Sellin & Pasricha, 2006). Each of these pharmaceutical substances are more beneficial for different types of cases in patients with the disease (Sellin & Pasricha, 2006). However, recent research has shown that prolonged use of antibiotics can disturb the balance of intra-intestinal bacteria flora, resulting in the worsening of the pathogenesis (Guarner & Malagelada, 2003). Probiotics supplements have demonstrated an efficacy to restore this balance by populating the intestines with the bacteria lost through prophylaxis with antibiotics (Cary & Boullata, 2010; Damaskos, & Kolios, 2008; D'Souza, Rajkumar, Cooke, & Bulpitt, 2002; Gionchetti et al., 2006; Guarner & Malagelada, 2003; Kanauchi, Mitsuyama, Araki, & Andoh, 2003; Kwon & Farrell, 2003; Quigley, & Quera, 2006; Sans, 2009; Sartor, 2004; Kruis, 2004).

If the patient must be hospitalized in order for the disease to be suppressed, enteral nutrition is commonly advised (Tsujikawa, Andoh, & Fujiyama, 2003). A recent study conducted by the Department of Gastroenterology at Nagoya University Graduate School of Medicine in Nagoya, Japan, reported a significant decrease in hospital admissions from complications in CD patients due to improvement through enteral nutrition targeting a specific

caloric intake (Watanabe et al, 2010). Caution must be taken though, as it has long since been discovered that this can lead to a severe selenium deficiency if the treatment is maintained over a long period of time (van Rij, Thompson, McKenzie, & Robinson, 1979; Sikora, Spady, Prosser, & El-Matary, 2011). However, this deficiency can be corrected by selenium supplementation (Baker et al., 1983).

Surgery is considered if the bowel becomes necrotic or if there is evidence of a perforation. Surgeons and gastrointestinal specialists concur that this must be viewed as a last resort, for the bowel does not regenerate and is very sensitive to invasive procedures. Because of this, all treatment options are usually exhausted before surgery is considered, excluding cases of extreme circumstances such as trauma or complete perforation (Peyrin-Biroulet et al., 2011; Slattery, Keegan, Hyland, O'donoghue, & Mulcahy, 2011).

Alternative Treatment

As research concerning the contributing factors of CD continues to develop, the involvement of diet and nutrition have been established as relevant components (Lucendo & De Rezende, 2009). A study in *The European Journal of Clinical Nutrition* found carbohydrate consumption to be much higher in CD patients than in comparative control groups (Geerling, Badart-Smook, Stockbrügger, & Brummer, 2000). There has been speculation that a diet primarily consisting of processed foods could be a risk factor for CD. There have been studies from as early as 31 years ago reporting increased intake of refined sugars in patients with CD (Mayberry, Rhodes, & Newcombe, 1980; Thornton, Emmett, & Heaton, 1979). Another study following patients placed on a dietary regimen of unrefined carbohydrates reported an 80% decrease in hospitalization when compared to a control group of patients without dietary guidelines (Heaton, Thornton, Emmett, 1979). Additional research not only supports the excess of refined sugars in the diet as a risk factor for CD, but a lack of raw fruits in vegetables in the diet as well (Thornton et al., 1979).

Naturopathic physicians also advise nutrition for the treatment of CD, only they suggest nutrient rich foods such as fruits and dark green vegetables as well as orthomolecular doses of certain minerals including magnesium, selenium, and zinc (Rannem, Ladegoded, Hylander, Hegnhoj, & Jarnum, 1992). Nutritional therapy can be very useful in the treatment of CD, especially in the case of children. It has been cited as a successful treatment in the control of inflammation and mucosal healing, exhibiting positive benefits to growth and overall nutritional status with minimal adverse effects (Hartman, Eliakim, & Shamir, 2009). Recently published research reveals the advantages of elemental diet as a maintenance treatment for CD (Takagi et al., 2006). This has been

shown to be beneficial in lowering the rate of relapse in patients, as well as provide an alternative for those that cannot tolerate pharmaceuticals such as thiopurines (Takagi et al., 2006). Research by Rajendran and Kumar (2010) demonstrates successful remission in patients with CD by eliminating foods causing unwanted reactions from the diet. They hypothesize that remission may be achievable through this method entirely, without reliance upon pharmacological aids.

Conclusion

There is still no known cure for CD, although there are several treatment theories available for the condition. Comparatively, we know very little about CD versus other chronic diseases. Because of this, future research is needed to understand the etiological factors, treatment options, and preventive approaches to the disease. This includes biomedical research and investigations concerning not only the pathophysiology on a molecular and cellular level, but also a holistic approach to treatment. Through research, we have seen that allopathic treatment can help patients gain remission quickly, but soon after patients fail to maintain this status. Moving forward, holistic practitioners continue to question the possible treatment options through rigid medical nutrition therapy, as well as herbalism and naturopathic medicine. As the prevalence of CD increases, it has become more evident that future research is needed to create efficacious treatment options, eventually resulting in a cure.

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