

Genetic, diet and pathogenic factors in ulcerative colitis

Murtaza Mustafa¹, Jayaram Menon², R.K. Muniandy³, TS. Tan⁴, M. Arif⁵.

^{1,3,4,5}Faculty of Medicine and Health Sciences, University Malaysia, Sabah, Kota Kinabalu, Malaysia, Sabah,

²Department of Gastroenterology, hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia.

Abstract: Ulcerative colitis (UC) is an idiopathic (autoimmune) inflammatory bowel disease, limited to the colon. UC affects the colon and rectum, while Crohn's (CD) affect the whole gastrointestinal tract (GIT). Highest incidence of UC was in Northeast England, Norway, Minnesota, Scotland, Faroes, Iceland and Denmark. The western diet lifestyle increases the incidence of UC. Risk factors in UC include, age, smoking, diet, breastfeeding, oral contraceptives, accutane use, sulfate producing bacteria, genetic factors, autoimmune disease, and psychological factors. Bacterial and parasitic infections can produce clinical findings as idiopathic UC. Macrophages and other accessory cells are an important component of the immune response in inflammatory bowel disease (IBD). Frequent clinical symptoms of UC is diarrhea which is usually associated with mucus and blood in stool. UC is associated with a general inflammation process that affects many parts of the body. Extra intestinal symptoms are the earlier signs of the disease, such as arthritis. UC is characterized as mild, moderate and fulminant disease continuous bleeding, toxicity, and colonic dilation. Diagnosis is on clinical grounds by significant findings on procto-sigmoidoscopy, colonoscopy, biopsy, and stool tests negative for infectious agents. Treatment is with 5-ASA drugs, proctocolectomy may be necessary in rare cases. Complimentary medicines and avoiding foods rich in sulfur amino acids-milk, cheese, eggs have proven benefits.

Keywords: Ulcerative colitis, Genetic, Autoimmune disease, and Management.

I. Introduction

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD). IBD (Crohn's disease (CD) and UC is often confused with irritable bowel disease [1]. UC only affects the colon and rectum, leaving the rest of the gastrointestinal tract unscathed, while Crohn's disease can affect the whole GI tract from mouth to anus [1]. UC is a chronic idiopathic inflammatory bowel disease characterized by diffuse mucosal limited to the colon [2]. The incidence of ulcerative colitis in North America is 10-12 cases per 100,000 per year, with peak incidence between ages 15 and 25, and thought to be bimodal distribution in age of onset in the 6th decade of life [3]. Studies has not revealed any difference in overall risk of dying in patients with UC from that of the background population. The disease primarily affects quality of life, and not the life span [4]. The highest incidence of UC in the United States, Canada, United Kingdom, and Scandinavia. Higher incidences are seen in the northern locations compared to southern locations in Europe and the United States [5,6]. The rates tend to be higher in more affluent countries, which may indicate increased prevalence is due to increased rates of diagnosis [7]. The industrial and Western diet lifestyle increases the prevalence of this disease [7]. UC has no known cause (idiopathic), there is a presumed genetic component to susceptibility to susceptibility [7]. Like Crohn's disease, UC is both classed as and managed as an autoimmune disease [7]. The main symptom of active disease is usually constant diarrhea mixed with blood, of gradual onset [1]. Management is with anti-inflammatory drugs, immunosuppression, and biological therapy targeting specific components of the immune response. Colectomy (partial or total removal of the large bowel through surgery) is occasionally necessary if the disease is severe, does not respond to treatment, or if significant complications develop [7]. A total proctocolectomy can cure ulcerative colitis as the disease affects the large bowel, and rectum and does not recur after removal of the later. While extra-intestinal symptoms will remain, complications may develop [7]. The paper reviews the current notions, genetic, diet and pathologic factors of ulcerative colitis.

II. Incidence Worldwide

The highest reported annual incidence of ulcerative colitis was in Northeastern England, 15 per 100,000 population [8]. Elsewhere, incidence rates were high in Norway [9], Minnesota [10], Scotland, Faroes, Iceland and Denmark [11-14]. Intermediate rates were reported in central and southern Europe [15]. Low rates are reported in the mid-to- southern United States [16]. Italy and Kuwait. Kuwait had the lowest reported annual incidence rate 1 per 100,000 population [17,18]. With some exceptions, the incidence rate of ulcerative colitis appears to vary directly with latitude. The highest reported rates generally occur in areas distant from equator. Latitude account for nearly 40 percent of geographic variation in incidence rates The main exception was Japan which is between 31 and 45°N. The geographic distribution of UC parallels that of colorectal cancer [19]. The latitude gradient in

incidence of UC has not always been a feature of this disease. For example, rates in Norway have climbed steeply since 1960s [20]. The trend is especially evident in western Norway; northeastern Scotland including Orkney and Shetland Islands, and in Faroes, where the incidence rate rose from 2 per 100,000 population during 1964 to 1986 to 13 during 1979 to 1983 ($P < 0.01$) [11,12].

Incidence rates in the Jewish population groups vary, in Baltimore was the highest ever reported in Jews, about four times the incidence of in the non-Jewish population. [21]. Low incidence rates in Jews in Israel are consistent with the latitude gradient characteristics of UC. Highest rates previously reported in Jews in Cape Town, South Africa, may partly be due to incidence in Jews who migrated from Germany and other European countries at high altitudes [22]. Incidence of UC is related to migration. For example, the incidence of UC was twice as high in Jews who migrated to Israel from Europe and the United States as in Jews born in Israel; the difference was most pronounced from ages 15 through 29 years, where the incidence rate in migrant Jews was three times that of resident Jews [23]. As with Crohn's disease, the prevalence of ulcerative colitis is greater among Ashkenazi Jews and decreases progressively in other persons of Jewish descent, on-Jewish Caucasians, African, Hispanic, and Asians [24].

III. Risk Factors

Age. Incidence of UC generally peaks at age 25 through 35 years again at 70 and older. Most studies of UC have reported bimodal age incidence, although some studies have reported a unimodal pattern [25]. The most prominent bimodal pattern of incidence has been reported from the United States, with incidence peaks at approximately ages 25 and 75 years in men, and 35 years and again in later life in women [16]. Another U.S. study reported prominent peaks at about age 25 and 65 years in men and 35 and 70 years in women [26].

Smoking. Heatley and colleagues [27], and Harriers and associates [28], noticed that there were few patients with UC who were current smokers of cigarettes, a number of case-control studies have verified these observations [29]. In several studies it was noted that former smokers were at higher risk for UC than those who had never smoked or those who smoke currently [30]. A meta-analysis of 12 case-control studies reported a combined odd ratio of 1.33 for former smokers compared with those who never smoked ($P < 0.01$) [31]. However, some studies showed former smokers to be at similar or only slightly higher risk than those who never smoked [32]. The association between not smoking and UC is strong and highly reproducible suggesting that there may be an agent in tobacco smoke that reduces the incidence and severity of the disease [29]. The agent has not been identified. Inhaling cigarette smoke depletes arachidonic acid, so less of substrate is available for synthesis of inflammatory mediators that may play a causal role [33]. Ulcerative colitis practice guidelines in adults contend that smokers have higher risk of Crohn's disease and lower risk of UC [34].

Diet. The colon is exposed to many dietary substances which may encourage inflammation; dietary factors have been hypothesized to play a role in the pathogenesis of both UC and Crohn's disease. There have been few studies to investigate such an association, one study showed no association of refined sugar on the prevalence of UC [35]. There is little evidence to date that dietary deficiency of insoluble fiber is a factor in UC or Crohn's disease. Japan where polished rice is consumed in preference to that containing bran, has low incidence rate of UC [36]. High intake of unsaturated fat and vitamin B6 may enhance the risk of developing UC [37]. Intake of saturated fat also may not explain the geographic pattern, since New Zealand Maoris, in whom UC is rare, are believed to consume large proportion of calories as saturated fat [38]. Other identified dietary factors that may influence the development and/or relapse of the disease include meat protein and alcohol beverages [39]. Another study demonstrated association with milk allergy [40]. Specifically, sulfur has been investigated as being involved in the etiology of UC, but this is controversial [41]. Sulfur restricted diet have been investigated with UC and animal models of disease. The theory of sulfur as an etiological factor is related to the gut microbiota and mucosal sulfide detoxification in addition to the diet [42].

Breastfeeding. There has been conflicting reports of protection of breast feeding in the development of inflammatory bowel disease. One Italian study showed a potential protective effect [43].

Oral contraceptives. Corrao and colleagues in a series of 819 cases of IBD (594 ulcerative colitis: UC and 225 Crohn's disease: CD), concluded that females who reported use of oral contraceptives for at least one month before onset of symptoms had a higher risk of CD, whereas no significant risk was observed for UC [43]. UC has been reported to improve on discontinuation of oral contraceptives [44].

Accutane a possible trigger of Crohn's disease and UC in some individuals. Three cases in the United States have gone on trial thus far, with all three resulting in multi-million dollar judgement against the makers of isotretinoin. There were an additional 425 cases pending as of [45].

Sulfate-reducing bacteria and hydrogen sulfide in the intestine. Levels of sulfate-reducing bacteria tend to be higher in persons with UC. An alternative theory suggests that the symptoms of the disease may be caused by toxic effects of the hydrogen sulfide on the cells lining the intestine [46].

Genetic factors. Genetic component to the etiology of ulcerative colitis can be hypothesized on the factors that include [47]: (a) aggregation of ulcerative colitis in families (b) identical twin concordance rate of 10%

and dizygotic twin concordance rare of 3%(c)ethnic differences in the incidence, and(d) genetic markers and linkage[48].From a genetic viewpoint UC and Crohn's disease sometimes behave as a single disease[49].The incidence of UC or Crohn's disease in close family members of patients(parents, sibling,or children) with inflammatory bowel disease has been reported as two to three times the expected rates. This estimate may be high, however, because some studies have accepted invalidated reports of inflammatory bowel disease in relatives[50].Sixteen identical twin pairs in which at least one twin had UC were identified among 25,000 same sex pairs in the Swedish twin registry, based on a central national diagnosis registry. Only one of the twin pairs was concordant for the disease [48].Despite the tendency for inflammatory bowel disease to occur in families,60 to 90 % of patients have no first -degree relative with the disease, and pedigree studies have failed to detect any known Mendelianpattern[51,48].

There are 12 regions of the genome that may be linked to UCV, including, in the order of their discovery,chromosomes16,12,6,14,5,19,1 and 3[52],but none of these loci have been consistently shown to be at fault, suggesting that the disorder arises from the combination of multiple genes. Forexample, chromosome band 1p36 is one such region thought to be linked to inflammatory bowel disease[53].Some of the putative regions encode transporter proteins such as OCTN1 and OCTN2.Other potential regions involve cell scaffolding proteins such as MUGUK family. There may be even human leukocyte antigen associated at work .In fact this linkage on chromosome 6 may the most convincing and consistent of genetic candidate[51].Multiple autoimmune disorders have been recorded with neurovascular and cutaneous genetic prophyrias including UC,,Crohn's disease, dermatitis herpetiformis,diabetes,systemic discoid lupus,rheumatoid arthritis, ankylosing spondylitis,scleroderma,Sjorgen's disease and scleritis.Physicians should be on high alert for prophyrias in families with auto-immune disorders and care must be taken with potential prophyrinogenic drugs,including sulfasalazine [52].

Autoimmune disease. Ulcerative colitis is an autoimmune disease characterized by T-cells infiltrating the colon[54].In contrast to Crohn's disease, which can affect areas of gastrointestinal tract outside colon ,UC usually involves the rectum and is confined to colon, with occasional involvement of the ileum.This so called"backwashileitis" can occur in 10-t0 20% of patients withpancolitis and is believed to of little clinical significance [24].UC can also be associated with comorbidities that produce symptoms in many areas of the body outside the digestive system. Surgical removal of the large intestine often cures the disease [34].

Psychological factors.The influence of psychological factors on ulcerative colitis has been reviewed[55]Case-control studies have reported no correlation between the number of stressful events and incidence of the disease, either in children or in adults[56,57].There are no personality traits that reliably differentiate people with UC from the unaffected population or those with Crohn's disease[55].

IV. Pathogenesis

Bacterial and parasitic infections can produce clinical findings indistinguishable from idiopathic UC[58].Macrophages and other accessory cells are an important component of the immune response inIBD.Macrophage recruitment in UC is facilitated by upregulation of macrophage chemotactic proteins(MCP) and increased IL-2R expression [59].Activated macrophages produce IL- β ,IL-6,TNF- α ,and IL-8,which augment the immune response in IBD[60].Elson and colleagues concluded that cytokines response in CD is associated with T_h17 in T-mediated model in mice,whereas in UC cytokine response is vaguely associated with T_h2[61].

An increased amount of colonic sulfate-reducing bacteria has been observed in some patients with UC,resulting in higher concentrations of toxic gas hydrogen sulfide[46].Human colonic mucosa is maintained by the colonic epithelial barrier and immune cells in the lamina proporiaN-butyrate, a short chain fatty acid,gets oxidized through the beta oxidation pathway into carbon dioxide and ketone bodies.It has been shown that N.butyrate helps supply nutrients to this epithelial barrier.Studies have proposed that hydrogen sulfide plays a role in impairing this beta oxidation pathways by interrupting the short chain acetyl CoA dehydrogenase an enzyme within the pathway.Furthermore, it has been suggested that protective benefit of smoking in UC is due to the hydrogen cyanide from cigarette smoke reacting with hydrogen sulfide to produce the nontoxic isothiocyanate, thereby inhibiting sulfides from interrupting the pathway[62].An unrelated study suggested that the Sulphur contained in red meats and alcohol lead to an increased risk of relapse for patients in remission[46]A role of colonic sulfide in the pathogenesis and treatment of UC has emerged based on biochemical, microbiological, toxicological, epidemiological,and therapeutic evidence. Sulfurfor fermentation in the colon is essential for N-butyrate formation and sulfidogenesis aids disposal of colonic hydrogen produced by bacteria.The number of sulfate reducing bacteria and sulfidogenesis is greater in UC than control cases.Sulfide is mainly detoxified by methylation in colonic epithelial cells and circulating red blood cells[46].The enzyme activity of sulfide methylated is higher in red blood cells of UC patients than control cases[46].

V. Clinical Manifestations

The Dominant symptoms of UC is diarrhea, which is usually but not always, associated with blood in stool [63]. Although the diarrhea is the dominant feature, some patients, especially elderly, complain of constipation [64]. In these patients, rectal spasm can prevent the passage of stool. The first attack in 27% of UC patients is of moderate severity [58]. The frequent clinical presentation of UC depends on the extent of the disease process [3]. Patients with diarrhea mixed with blood and mucus, of gradual onset that persists for an extended period. They may also have weight loss and blood on rectal examination. The inflammation caused by the disease along with chronic loss of blood from GI leads to increased rates of anemia. The disease may be accompanied with different degrees of abdominal pain, from mild discomfort to painful bowel movements or painful abdominal cramping with bowel movements [3]. UC is associated with a general inflammation process that affects many parts of the body. Sometimes these associated extra-intestinal symptoms are the initial signs of the disease, such as painful arthritic knees in a teen aged and may be seen in adults also. The presence of the disease may not be confirmed immediately, however until the onset of intestinal manifestations [3].

UC affects the colon and the rectum, and classifications of UC include:[34].

- Distal colitis, potentially treatable with enemas
- Proctitic: Involvement limited to the rectum
- Proctosigmoiditis: involvement of the recto sigmoid colon, the portion of the colon adjacent to rectum
- Left -sided colitis: Involvement of the descending colon, which runs along the patient's left side, up to the splenic fixture and the beginning of the transverse colon.
- Extensive colitis, inflammation extending beyond the reach of enemas: Pancolitis: Involvement of the entire colon, extending from the rectum to the cecum, beyond which the small intestine begins.

In addition to the extent of involvement, people may also be characterized by the severity of their disease i.e., mild disease, moderate disease, severe disease and fulminant disease correlates with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion) [34].

UC is believed to have a systemic (i.e., autoimmune) origin, patients may present with comorbidities leading to symptoms and complications outside colon. The frequency of such extra intestinal manifestations has been reported as anywhere between 6 to 47 percent, these include:[65]. a) **Aphthous**-ulcer of the mouth, b) **Ophthalmic**-Iritis or uveitis, which is inflammation of the eye's iris, and **Episcleritis**, c) **Musculoskeletal**-Seronegative arthritis, which can be a large-joint oligoarthritis (affecting one or two joints), or may affect many small joints of the hands and feet, **Ankylosing** spondylitis, arthritis of the spine, **Sacroilitis**, arthritis of the lower spine, **Cutaneous**-Erythema nodosum, which is a panniculitis, or inflammation of the subcutaneous tissue. **Pyodermagangrenosum**, which is a painful ulcerating lesion involving the skin. **Deep venous thrombosis**. **Autoimmune** hemolytic anemia, **Clubbing**, a deformity of the ends of the finger. **Primary sclerosing cholangitis**, a distant disease that causes inflammation of the bile ducts.

VI. Diagnosis

The diagnosis of UC is suspected on clinical grounds and supported by the appropriate findings on proctosigmoidoscopy or colonoscopy, biopsy and by negative stool examination for infectious agents [59].

Diagnostic workup include [34,66], complete blood count to exclude anemia; thrombocytosis, a high platelet count, is occasionally present electrolytes, (serum) studies, chronic diarrhea may be associated with hypokalemia, hypomagnesemia and pre renal failure, liver function test (LFT) to screen for bile duct involvement: primary sclerosing cholangitis, erythrocyte sedimentation rate (ESR), elevated ESR indicating an inflammatory process is present C-reactive protein (CRP) elevated level being another indication of inflammation, X-rays, urinalysis, and stool culture to exclude parasites and infectious agents. Although ulcerative colitis is a disease of unknown causation, inquiry should be made to unusual factors believed to trigger the disease. The factors may include: recent cessation of tobacco smoking, recent administration of large doses of iron or vitamin B6, hydrogen peroxide in enemas or other procedures [34].

Endoscopy is a gold standard for diagnosis of UC. Endoscopic findings in UC include, a) loss of the vascular appearance of the colon) superficial ulceration, which may be confluent and pseudopolyps. UC is usually continuous from the rectum, with the rectum almost universally being involved. There is rarely perianal disease, but cases have been reported, The degree of involvement endoscopically ranges from proctitis or inflammation of rectum, to left sided colitis, topocolitis, which is inflammation involving ascending colon [34].

Histological studies. The pathology in ulcerative colitis typically involves distortion of crypt architecture, inflammation of crypts (cryptitis), frank crypt abscesses, and hemorrhage or inflammatory cells in the lamina propria. In cases where clinical picture is unclear, the histomorphologic analysis often plays a pivotal

role in determining the diagnosis and thus the management. By contrast, a biopsy analysis may be indeterminate, and thus the clinical progression of the disease must inform its treatment [34].

The most common disease that mimics the symptoms of UC is Crohn's disease, as both are inflammatory bowel diseases that can affect the colon with similar symptoms. It is important to differentiate these diseases, since the course of the diseases and treatment may be different. In some cases, however, it may not be possible to tell the difference, in which case the disease is classified as indeterminate colitis [34]. Other similar conditions (as UC) should be excluded i.e., Crohn's disease, infectious colitis, *Clostridium difficile*-associated colitis, ischemic colitis, radiation colitis and chemical colitis [34].

Specialized diagnostic tests. Macrophages and other accessory cells are an important component of immune response in IBD. Macrophages recruitment in UC is facilitated by upregulation of macrophage chemotactic protein (MCP) and increased IL-2R expression [67]. Activated macrophages produce IL- β , IL-6, TNF- α , and IL-8 which augment the immune response in immune in IBD [69]. Anti-neutrophil cytoplasmic antibodies (ANCA) are detected in the sera of patients with UC and Crohn's disease. The clinical utility of ANCA in IBD is unclear [67].

VII. Management And Treatment

Ulcerative colitis can be treated with a number of medications including 5-ASA drugs such as sulfasalazine and mesalazine. Corticosteroids such as prednisone can also be used due to their immunosuppressing and short term healing properties, but due to risk outweighing the benefits, they are not used long term treatment. Immunosuppressive such as azathioprine, and biological agent such as infliximab and adalimumab are given lastly, only if people cannot achieve remission with 5-ASA and corticosteroids, due to their possible risk factors, including, but not limited to increased risk of cancers in teenagers and adults [68]. Sulfasalazine has been a major agent in the therapy of mild to moderate UC for over 50 years. In 1977, Mastan S. Kalsiet al determined that 5-aminosalicylic acid (5-ASA and mesalazine) was the therapeutically active in sulfasalazine [69].

The action of 5-ASA in UC have been reviewed and indicate that 5-ASA reacted with numerous agents as well as products of inflammatory cells [70]. That 5-ASA can reduce the fermentation production of sulfide from sulfur amino acids was first reported in 1994 [71]. Antibiotic gentamicin inhibits the activity of sulfate reducing bacteria in the colon, which presumably reduces sulfide production [72]. Detoxification of sulfide by colonic epithelial cells requires S-adenosyl methionine (SAM) and ATP [73]. The level of SAM are low in colonocytes in active UC and it appeared worthwhile to boost the capacity of colonocytes to detoxify sulfide [74]. Attempts to boost methanogenesis and suppress sulfate-reducing bacteria has been undertaken using a variety of agents. Sodium molybdate was found to reduce sulfate reducing bacteria [75].

Complimentary medicines. Studies using a transdermal nicotine patch have shown clinical and histological improvements [76]. Parenteral iron supplementation to be used first line as patients respond quicker in anemia, is associated with fewer gastrointestinal side effects and is not associated with compliance issue [77]. In vitro research, animal evidence, and limited human study suggest that melatonin may be beneficial [78]. Dietary fiber, meaning indigestible plant matter, has been recommended for decades in the maintenance of bowel function. Oatmeal is also been prescribed [79]. Fish oil and eicosapentaenoic acid (EPA) derived from fish oil, inhibits leukotriene activity, the latter may be a key factor of inflammation [80]. Vinay and colleagues contend traditional Ayurved therapies like Pichaha Basti, Anuvasan Basti, internal medications along with external therapies like Parishecham, Gudaprakshalan, Pichu in UC with beneficial affects [81].

Surgery or proctocolectomy may be necessary in event of: exsanguinating hemorrhage, frank perforation or documented or strongly suspected carcinoma. Surgery is also indicated for patients with severe colitis or toxic mega colon. Patients with symptoms that are disabling and do not respond to drugs may wish to consider whether surgery would improve the quality of life. UC is a disease that affects many parts of the body outside the intestinal tract. In rare cases the extra-intestinal manifestation of disease may require removal of the colon [34]

Prevention. Truelove's original work indicated that withdrawal of milk, eggs and cheese conferred a therapeutic benefits on UC [82]. Removing foods rich in sulfur amino acids (milk, eggs, cheese) has proven benefits in UC [46].

VIII. Conclusion

Ulcerative colitis (UC) and Crohn's disease (CD) both are inflammatory bowel diseases that can affect the colon with similar symptoms. It is important to differentiate these diseases, since treatment may be different. UC is disease of unknown causes, with genetic, diet, and environmental factors play an important role. UC can be treated with 5-ASA drugs such as sulfasalazine and mesalazine, with corticosteroid added. Proctocolectomy may be indicated in perforation or suspected carcinoma.

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