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Lecture

Environmental Factors in IBD

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SUMMARY

A large number of environmental factors have been implicated in the pathogenesis and development of IBD. The epidemiological data are strong and are reproducible only for smoking and appendectomy, whereas the importance of other risk factors, such as breast-feeding, contraceptive and NSAIDs use and sugar intake are sharply divergent. Nevertheless, the mechanism for the effects of all these studied environmental factors remains unknown and the interplay between these exogenic factors and genetic subtypes of IBD is under investigation.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD), the primary constituents of inflammatory bowel disease (IBD), are precipitated by a complex interaction of environmental, genetic and immunoregulatory factors. Over the past few years, several clinical and experimental studies suggest that genetic factors contribute to susceptibility of IBD. IBD seems to be multigenic, with the most clearly established genetic link between certain NOD2 variants and CD.[1,2] Nevertheless, whatever part the genetic loci play in conferring susceptibility to IBD, studies in twins make it clear that the development of disease depends on additional factors. Moreover, many epidemiological studies have shown that concerning the prevalence of IBD, racial gaps are closing quickly and there has been a remarkable increase in the incidence of IBD, and CD in particular, during the last half century. These observations point to changes in the environment as major culprits of these evolutions, since genetic variations are negligible in such a short period of time. Among myriad factors studied, the most important environmental factors for which there is an evidence-based link to IBD pathogenesis are the following:

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1. Smoking

The most significant and the best documented environmental factor identified for IBD is tobacco use, particularly cigarette smoking. Smoking has an opposite effect on UC and CD, supporting the notion that distinct mechanisms underlie the pathogenesis of each form of IBD.[3] UC is largely a disease of ex-smokers and nonsmokers, whereas CD is associated with smoking. Cessation of smoking increases the risk of developing UC, supporting its protective role in this disease. However, a recent study from Spain found that UC patients who smoke have an increased risk of extraintestinal manifestations (seronegative spondyloarthropathy and dermatological complications such as pyoderma gangrenosum and erythema nodosum) in comparison with nonsmoking patients.[4] Contrary to findings in UC, cigarette use in CD patients increases the frequency of disease relapse and need for surgery, and discontinuation improves the disease course. The role of passive smoking in IBD, is still under evaluation. A large scale multicentre study from Israel did not find any association between passive smoking and IBD, but when a quantative exposure index was used, UC patients were found to be less exposed to passive smoking than the community controls.[5]

The mechanism for the effects of smoking on IBD is unknown. Researchers have studied the systemic effects, cellular and humoral immune effects, mucosal changes, and the intestinal permeability changes with IBD and smoking. To date, none of these studies adequately explains the observed clinical patterns. Smoking alters the ratio of T-helper to T-suppressor cells, reduces T cell proliferation, modulates apoptosis and significantly de-

creases serum and mucosal immunoglobulin levels. In animal models, smoking reduces mucosal cytokine production and promotes adhesion of leukocytes to endothelial cells. Furthermore, it enhances small bowel permeability and colonic mucus production. Transdermal nicotine shows some beneficial effect in patients with mild to moderate UC, but in patients with CD, nicotine may contribute to the hypercoagulability state present in this condition, and therefore nicotine avoidance is strongly recommended in this group of patients.[6]

2. Appendectomy

UC patients have a low rate of appendectomy, and appendectomy lowers the risk of developing UC, primarily for patients under the age of 20 years who had the procedure because of acute inflammation.[7] On the contrary, appendectomy has been recently associated with an increased risk of developing CD. In particular, this increased risk is present in female subjects who had appendectomy more than 20 years ago. It has to be mentioned that a history of perforated appendicitis predicts a worse clinical outcome.[8]

3. Drugs

Oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs) are the two main classes of drugs that have been intensively studied for a possible epidemiological or cause-and-effect relationship with IBD. Many, but not all, studies have discerned an increased risk (about twice) for CD among women who use oral contraceptives.[9] There has been controversy regarding whether women using these drugs have worse clinical outcome. Low doses seem to be safe, but considering the hypercoagulability state present in CD, the concomitant use of these drugs may aggravate the risk of thromboembolic events, and therefore it's preferable to be avoided. NSAIDs have been implicated not only in exacerbations of IBD, but also as a potential precipitant of new cases, perhaps by blockade of protective prostaglandins, by altering mucosal immune reactivity and by increasing intestinal permeability.[10]

4. Dietary factors

Traditionally, a potential relationship between components of the diet and disease pathophysiology has been long considered and immunological mechanisms have been postulated to link food antigens and the development of intestinal inflammation. However, this logical explanation is far from proven. Among the analyzed dietary factors some reports suggest that refined sugar consumption might be a risk factor for CD, but not UC.[11] In a large multicentre study from Japan, higher consumption of sweets was positively associated with UC risk, whereas the consumption of sugars and sweeteners, fats and oils, fish and shellfish, were positively associated with CD risk. In respects to nutrients, the intake of vitamin C was negatively related to UC risk, while the intake of total fat, monounsaturated and polyunsaturated fatty acids, vitamine E, and n-3 and n-6 fatty acids were positively associated with CD risk.[12] A paucity of fresh fruits, vegetables and fibers in diet have been associated with the development of CD,[13] whereas there is good evidence supporting the benefits of elemental diets as both primary or adjuvant therapy for CD. Titanium oxide in the diet, primarily as an ingredient of toothpaste, has been implicated in the development CD. Titanium oxide microparticles may act as an absorbent for lipopolysaccharide and may lead to markedly heightened lymphocyte responses.[14]

5. Breast-feeding

Most studies have found breast-feeding to be protective in UC and CD, presumably by playing a role in early programming of immune responses in the developing gastrointestinal tract. A nationwide case control study in Italy found significantly increased risks of UC (OR:1.5, CI:1.1 to 2.1) and CD (OR:1.9, CI:1.1 to 3.3) in patients who had not been breast-fed.[15] A shorter duration of breast feeding has been shown to be associated significantly with increased risk of CD. Nevertheless, other investigators have found varying results, such as significant association only with UC, others only with CD and others no association at all.[16]

6. Hygiene, occupation and social status

This group of interrelated factors is large and difficult to analyze. UC and CD appear to be more common in higher socioeconomic status classes, in developed countries compared with underdeveloped countries and in urban areas in comparison with rural areas. Data in both Europe and North America have described a "North-South" gradient in IBD, but these differences trend to narrow, due to an increase in southern regions and stabilization in northern areas.[17] Outdoor workers have less risk of developing IBD than individuals with indoor occupations and sedentary workers are at higher risk for IBD. A number of theories have been advanced to explain these observations, but the reality is that the relationship of these parameters with IBD is currently obscure.

7. Stress

Many patients report a correlation between disease

exacerbations and stress. The specific mechanisms underlying stress-induced disease exacerbation are uknown, but a complex interplay of nervous, endocrine and immune factors is likely to be implicated.[18] Some studies have shown that stress augments the intestinal permeability and the entry of excessive amounts of luminal antigens could activate pre-sensitized mucosal T cells. However, stress is more likely to modulate disease manifestations rather than being an initiating factor.

8. Microbial factors

Several microorganisms (*Listeria monocytogenes, Chlamydia trachomatis, Escherichia coli, Cytomegalovirus, Saccharomyces cerevisiae*, etc), have been proposed as having a potential etiologic role in IBD. More recently, *Mycobacterium paratuberculosis* in CD has been the center of major controversy and many studies on this topic yielded conflicting or inconclusive results.[19] Moreover, controlled trials have failed to show a therapeutic effect of antituberculous therapy in CD patients.[20]

A viral etiology has also been proposed as the cause of IBD, particularly for CD. Paramixovirus-like particles were found in CD endothelial granulomas leading to the suggestion that CD is a chronic vasculitis caused by the persistence of the measles virus in the mucosa. An association between perinatal measles and predisposition to CD was also observed in some epidemiological and serological studies, but these findings were not confirmed by later studies. The hypothesis that measles vaccination, rather than measles infection, might be a risk factor for CD was also raised, but again subsequent studies failed to confirm this association.[21]

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