

Epidemiology of intrafamilial inflammatory bowel disease throughout Europe

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Abstract

The incidence and prevalence of inflammatory bowel disease (IBD) have distinctly changed over the past decades throughout Europe. From former North-South and West-East risk gradients, nowadays, classic high-risk areas for IBD in North and West present more stable incidences whereas in formerly low-risk zones the incidence is rising. These changes cannot be explained by genetic modifications in IBD patients' background, which draws attention to the possible existence of potent environmental factors triggering this epidemiologic shift. Important lessons can be drawn from different European population-based studies assessing the influence of environmental factors in familial IBD that may impact on the outcome of the disease and the management of the patients and their relatives.

Keywords inflammatory bowel disease, epidemiology, familial aggregation, environmental factors

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Introduction

Inflammatory bowel disease (IBD) encompasses two chronic, complex relapsing diseases whose etiology is still uncertain: Crohn's disease (CD) and ulcerative colitis (UC). The chronic inflammation is thought to be caused by an excessive and poorly controlled immune response to the intestinal microbiota in genetically susceptible subjects. Concordance rates in twin pairs and siblings in population-based studies have provided strong evidence that genetic factors are important in disease pathogenesis [1] and thanks to the advent of genome-wide association scans; rapid identification of multiple susceptibility genes for CD and UC has been possible [2].

Epidemiology of IBD throughout Europe

Several studies have been conducted on the epidemiology of IBD showing that the incidence of IBD varies greatly

worldwide, with incidence rates of UC and CD varying between 0.5-24.5/10⁵ and 0.1-16/10⁵ inhabitants respectively and prevalence rates rising up to 396/100 000 inhabitants [3-5]. The highest incidence rates are recorded in North America and Northern and Western Europe, while lower rates are recorded in Africa, South America and Asia. Therefore, IBD seems to be more common in developed countries which points out to different environmental factors related to urbanization and industrialization in IBD [6].

Nevertheless, during the last decades the incidence of IBD appears to have changed. Previous studies in Europe suggested that the incidence was decreasing from north to south [7], but in the early 1990s the European IBD Study Group found comparable rates between Southern and Northern Europe [8]. The overall incidence reported per 10⁵ at ages 15-64 years was 10.4 for UC and 5.6 for CD. The age and sex adjusted rate in Northern countries was 11.8 per 10⁵ for UC and 7.0 for CD, in contrast with the 8.7 and 3.9 for UC and CD respectively in Southern countries. It is possible that the smaller than expected difference in North-South incidence of IBD found in this study may be explained by the relative stable incidence in previously high-incidence areas, whereas in formerly low-incidence areas the incidence continuously rose. A further difference is that the previously reported predominance of UC is diminishing, as CD is becoming more prevalent.

The same trend appears in the West-East European gradient. Western European countries are traditionally high-incidence areas but they have experienced a stabilization or even decrease in the incidence rates [9], while the disease has become more prevalent in previously low-incidence areas in East Europe, such as Hungary (incidence rates 11.0 per 10⁵ for UC and 4.7 per 10⁵ for CD) and Croatia (incidence

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rates 4.3 per 10⁵ for UC and 7.0 per 10⁵ for CD) where recent studies have reported sudden increases in IBD incidence and prevalence rates, comparable to that in Western European countries [10-12]. In contrast, studies from other Eastern European countries such as Czech Republic or Romania, with an incidence rate of 0.97 per 10⁵ and 0.50 per 10⁵ for UC and CD respectively, still report low incidence rates [13-15]. However, these incidence rates could be underestimated due to methodological shortcomings in these studies [12]. Although changes in lifestyle in Eastern Europe during recent years have lead to a more “westernized” standard way of living, the reason for these changes remains unknown. They could be due to increased awareness of the disease and differences in diagnostic practices, or they could mirror real differences, which might reflect environmental factors, lifestyle and genetic susceptibility [16]. Changes in the lifestyle in Eastern Europe during the last two decades have resulted in a more “westernized” standard way of living, meaning increased consumption of refined sugar, fatty acids, “fast food”, cereals and bread and reduced consumption of fruit, vegetables and fibers [17]. All these aspects of “westernization” have been previously associated with IBD in different studies [18,19] and therefore, “westernization” of lifestyle may be an explanation of the observed increase in the incidence of UC and CD. The previously mentioned EC-IBD study in Europe found comparable incidence rates between Northern and Southern Europe, but failed to provide an explanation of the geographic distribution of the diseases [4]. This could be due to the fact, that countries from Eastern Europe were not included in the study, thus supporting the idea of a developed-developing gradient. IBD can be better distributed according to the development of countries, the underlying cause for such a distribution possibly being westernization, thereby explaining the increase of the incidence observed in Hungary and Croatia [17].

According to this, it would be of great interest to study the temporal trends for IBD in Eastern Europe, describe the real differences among geographical regions across Europe and, furthermore, demonstrate the real impact of life style on the incidence of IBD. In order to achieve these aims, an epidemiologic study throughout Europe is being conducted

in an attempt to explore the role of environmental factors in IBD pathogenesis and seek new risk factors [20].

Familial IBD

Familial IBD refers to the higher incidence of the disease among IBD relatives than expected by chance. Several studies, many of them throughout Europe, have assessed the familial aggregation of IBD and the different factors responsible for this fact. These population-based studies have shown that relatives of an IBD patient have a much higher risk to develop the same disease than the general population [1,21-23], (Table 1) and that this risk depends, mainly, on two factors: 1. degree of kinship; and 2. type of IBD.

Regarding the degree of kinship, the prevalence of IBD in first-degree relatives is higher than in second-degree, mainly in those with concordant disease [1]. The age-adjusted risk for IBD development in CD patients’ relatives was estimated in a study performed in Belgium, showing that the highest age-adjusted risk of IBD was found in offspring (10.4%) and that the age-adjusted empirical CD risk among first-degree relatives of patients with CD was higher in offspring (7.4%) than in parents, (1.9%) and slightly higher than in siblings (4.9%) [23]. Moreover, in a French population-based study, first-degree relatives of CD patients appear to have an increased probability of sharing the same disease phenotype, especially according to disease location and behavior [24]. Concordant results were found in a large Italian study in 128 families [25]. In this study, CD families displayed a high-rate concordance in disease location (46%), presence of extra-intestinal manifestations (67%) and behavior (75%). Regarding UC families, high concordant rates were found for extent of colon involvement (33%) and relapse rate (34%), but overall, rates of concordance in UC families were distinctly lower than those observed in CD families. However, a higher than expected concordance was demonstrated for ileal localization in CD families (40% of concordance compared to the 17% expected) and extensive colitis in UC families (22% compared to 9%). These data were in keeping with previous observations [26]. Furthermore, in this study it was demonstrated that the

Table 1 Studies assessing the familial aggregation of inflammatory bowel disease

Study Design	Country	Risk for concordant disease Among first-degree relatives	Year	Author
Population based	Denmark	10.0 fold in CD 8.0 in UC	1991	M Orholm [1]
Population based	UK	17-35 in CD 15 in UC	1993	CSJ Probert [21]
Case-control	Belgium	13 in CD	1996	M Peeters [23]
Population based	Sweden	15 in UC	1986	U Monsen [22]

CD, Crohn’s disease; UC, ulcerative colitis

symptoms and diagnosis of IBD were ascertained 15-20 years earlier in subsequent generations. This difference was found for both CD and UC families, in parent-child, and second-degree related families, pointing to the possibility of a genetic anticipation in IBD. The concept of genetic anticipation implies an earlier onset and increased severity as the disease is passed through subsequent generations, but there are difficulties in defining biological anticipation in polygenic disorders such as IBD, as the epidemiological data may be biased, particularly in retrospective series. Therefore, the possibility that IBD develops at an earlier age in offspring than in their parents is still a subject of debate [27-29].

Finally, with respect to the type of IBD, familial aggregation has been shown to be more frequent in CD patients than in UC in age-adjusted studies and there is also a trend towards association between CD patients and relatives with diagnosis of UC compared to UC patients and CD-affected relatives [1,23]. Although affected relatives can develop both forms of IBD, the greatest risk is associated with the appearance of the same disease type occurring in the index case [30].

Environmental factors in familial IBD

The significant changes in the incidence and prevalence of IBD that have taken place throughout Europe in the past decades cannot be explained by changes in the genetic background, but by the presence of potent environmental factors playing a key role in IBD pathogenesis. In this sense, several studies performed in different European countries have assessed the changes in IBD appearance in immigrant populations from low IBD risk regions to higher risk areas, but only a few of them have been focused on environmental risk factors related to familial IBD. Overall, it could be said that the risk of IBD development in immigrant populations from low to high IBD prevalence areas appears to be similar to the indigenous populations [31,32].

Diet

The largest controlled study assessing the role of environmental factors on familial IBD was performed in Belgium. In this study, 21 families with 3 or more first-degree relatives diagnosed of CD were investigated [33]. All the subjects in the study answered a wide range of questions that delved into first symptoms, childhood vaccinations and diseases, food items, potable water supplies, social activities, travel, pets, and home and surrounding environment. Affected families and controls presented some remarkable differences. There were significantly more smokers in the patients and their relatives than in controls and patients had more appendicitis during adolescence, ate less oats, rye, and bran than controls, and consumed more unpasteurized cheese. Patients drank significantly less tap water and more well water than controls. Furthermore, clustering of cases in time occurred in 13 of the 21 affected families. Taken together, these results show how

different dietary habits seem to influence gastrointestinal flora, the consumption of well water being an important risk factor for CD in this study.

In a different study by the same Belgian group, a large family who migrated from Morocco to Belgium with various cases of CD was analyzed [34]. Within the same family, 5 new cases of CD occurred after migration to Belgium. Known genetic variants associated with CD and serologic markers were studied in all family members, but no differences between cases and healthy family members were found. Therefore, the appearance of these new cases after migration cannot be explained by the known genetic susceptibility factors, which points to a possible major environmental factor. Similar cases, with similar conclusions, have been reported in migrant families in different European countries [35].

Gut microbiota

Van Kruiningen *et al* [36] analyzed the pedigrees, sibships, temporal relationships among cases and family circumstances relevant to the frequency or onset of CD in a group of patients with familial IBD. In this study, first-borns and subsequently born siblings were more frequently affected and a significant CD clustering in time was described that would indicate a contagious element in the etiology of CD. In a previous study by the same author [37] in an attempt to identify the suspected infectious cause, two French families with multiple CD cases were studied. Pathogens such as *Campylobacter*, *Yersinia*, *mycobacteria*, *mycoplasma* and animal enteropathogenic infections were all dismissed and no specific pathogens were found.

A general dysbiosis of the intestinal microbiota has been established in patients with CD [38]. In this sense, Joossens *et al* [39] recently performed a study on patients with CD, their unaffected relatives and matched controls in order to characterize this dysbiosis. This study demonstrated that unaffected relatives of patients with CD have a different composition of their microbiota compared with healthy controls. This dysbiosis is not characterized by lack of butyrate producing-bacteria as observed in CD [38], but suggests a role for microorganisms with mucin degradation capacity.

Research on twins has been of great interest assessing the role of genetic and environmental factors in familial IBD. In this sense, several studies have been published in different European countries. In Sweden and Denmark more than 300 twin pairs discordant for IBD diagnosis were included in a questionnaire-based study on environmental factors [40]. Recurrent gastrointestinal infections were associated with both UC and CD and hospitalization for gastrointestinal infections was associated with CD. These associations indicate that markers of possible infectious events may influence the risk of IBD. Some of these effects might be mediated by long-term changes in gut flora or alterations in reactivity to the flora. These findings are in keeping with an increased frequency of fecal-oral transmitted infections reported in multiplex CD families [33] and point out the possibility that past infections

might influence the risk of IBD.

Tobacco

It has long been known and repeatedly shown that patients with CD are significantly more likely to be smokers than the general population. It has also long been known that patients with UC are more likely to be ex-smokers than the general population and it has long been clinically observed that patients with UC who smoke are more likely to flare if they quit smoking. Moreover, it has been demonstrated that tobacco discontinuation improves CD course [41-43]. To further evaluate the role of tobacco in familial IBD, Bridger et al [44] in the UK, analyzed 658 IBD patients, including 339 affected siblings pairs of whom 89 were discordant for smoking when diagnosed. Smoking at diagnosis was associated with development of CD in all of the familial patients, with an increase in ileocecal disease, fibrostenosis, and intestinal resection when analyzed. Smokers were also protected from UC. Of 89 sibling pairs discordant for smoking at diagnosis, 23 were also discordant for disease type in 21 of these, CD occurred in the smoker and UC in the non-smoker. The explanation from the author of part of the apparent "protective" effect of smoking on sporadic UC is that perhaps the form of IBD that develops in a proportion of smokers is not UC but CD.

Conclusions

The chronic inflammation underlying IBD is probably caused by an excessive and poorly controlled immune response to different environmental factors, including gut microbiota, in genetically susceptible subjects. As the changes in the past decades in the incidence and prevalence of IBD throughout Europe cannot be explained by changes in genetic background, environmental factors are thought to be the underlying cause of these changes and therefore, they have become a major issue of discussion and research. These changing trends in the epidemiology of IBD provide an opportunity to examine possible etiological hypotheses but also give the physicians different approaches that can be undertaken in an attempt to impact on the course of familial IBD. In this sense, in at-risk families, where there are several affected family members, perhaps greater vigilance with antibiotic use in childhood and diet can be considered, as well as awareness to smoking cessation in CD.

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