

Changing Patterns in the Epidemiology of Crohn Disease

Moftah H Alhagamhmad, Steven T Leach, Daniel A Lemberg, Andrew S Day

Moftah H Alhagamhmad, Steven T Leach, Daniel A Lemberg, Andrew S Day, School of Women's and Children's Health, University of New South Wales Sydney, NSW, Australia

Daniel A Lemberg, Department of Gastroenterology, Sydney Children's Hospital, Randwick, Sydney, NSW, Australia

Andrew S Day, Paediatrics, University of Otago, Christchurch, New Zealand

Correspondence to: Andrew S Day, MB, ChB, MD, FRACP, AGAF, Professor and Head of Department, Department of Paediatrics, University of Otago, Christchurch, Christchurch, New Zealand.
Email: andrew.day@otago.ac.nz

Telephone: +64-3-364-0747

Fax: +64-3-378-6355

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INTRODUCTION

Crohn Disease (CD; also known as regional enteritis) is one form of inflammatory bowel disease (IBD)^[1]. CD can affect any part of the gastro-intestinal tract and is a chronic, episodic condition characterized by transmural inflammation and skip lesions. In 1932, the American gastroenterologist Burrill Bernard Crohn and his two colleagues Ginzberg and Oppenheimer, were the first to describe the disease in young patients with inflammation of the terminal ileum, and since then the disease has been referred to as Crohn disease^[2].

Pathologically, CD is a multi-factorial disease where the dysregulated immune response, a key hallmark of disease pathogenesis, is initiated by the combined effects of factors including environmental triggers, genetic predisposition and the intestinal microflora^[3]. Despite increased understanding of the roles of these key pathogenetic factors, the exact cause of CD remains unclear, and the condition remains incurable.

CD is now considered an emerging universal health problem affecting a large number of people throughout the world. Although CD is not considered a fatal disease, it significantly impairs the health, life quality, and psychosocial well-being of a substantial portion of affected patients^[4,5]. Further, CD is a disease with a significant cost burden related to health care utilization and productivity loss^[6]. It has been reported that there are at least 70,000 Australians living with IBD, with more than 41,000 cases of CD across the country^[7]. This report aims to summarise current incidence and prevalence trends of CD across the world, and to highlight the

ABSTRACT

Crohn disease is a chronic inflammatory disorder that primarily affects the alimentary tract. It is an increasingly global health concern, with recent data indicating rising rates across many countries in the world, along with a growing prevalence in childhood. Numerous reports indicate that Crohn disease is no longer confined to Western countries, with many reports of diagnosis in other regions including less developed nations. Changes in dietary patterns, along with other environmental factors, appear to account for these recent changes in the patterns of Crohn disease epidemiology. The objective of this work was to review current available literature concerning the epidemiology of Crohn disease and to consider the possible roles of environmental factors that may be implicated in these changing patterns. Widespread data indicates increasing incidence of Crohn disease in many countries across the world. The reasons for these rapid changes in the epidemiology of Crohn disease are not clearly understood. However, environmental changes appear to be the most important factors for these recent changes.

importance of putative environmental factors linked with the recent epidemiological patterns of this chronic disease.

INCIDENCE OF CROHN DISEASE

Historically, CD has been a condition seen exclusively in Western or developed countries. Recent reports show that the incidence of disease is rising in both developed and less developed countries including China, South Korea, India, Lebanon and Thailand^[8]. However, the incidence of CD remains higher in industrialized countries compared to developing countries.

Internationally, the incidence of CD ranges from 0.1 to 16 per 100,000 of the populations with higher rates recorded in Europe, the United Kingdom and North America, whilst lower rates are reported in Africa, South America and Asia^[9]. In North America, the incidence rates range from 3.1 to 14.6 per 100,000 of the population^[10], and in Europe the incidence is reported to be 9.8 cases per 100,000 of the population^[11]. In contrast, data from Saudi Arabia indicate an incidence of 0.94 per 100,000 of the population between 1983-2002^[9]. An even lower incidence rate was reported for Sri Lanka with an incidence of 0.09/100,000 inhabitants in 2008^[12]. Moderate incidence has been reported for Hong Kong, China with an incidence of 1.25 per 100,000 individuals in 2011^[13] and Korea, with an incidence approaching 5.1/100,000 for CD in 2008^[14].

The highest reported incidence rates worldwide come from Nova Scotia, Canada (incidence of 20.2 per 100,000 individuals in 2000)^[15], Geelong, Australia (incidence of 17.4 per 100,000 in 2008)^[7] and Canterbury, New Zealand (incidence of 16.5 per 100,000 of the population in 2004)^[16]. A more recent report population-based study from Nelson, New Zealand indicated an incidence of 15.2 per 100,000 inhabitants in 2012^[17].

PREVALENCE OF CROHN DISEASE

It has been estimated that the worldwide prevalence of CD is approximately 150 per 100,000 individuals^[18]. The prevalence rates tend to follow the incidence rates with highest rates described in developed countries. In North America the prevalence varies from 44 to 201 per 100,000 of the population^[19]. For instance, in the USA the prevalence of CD was 244 per 100,000 inhabitants in 2004, which considered one of the highest prevalence rates worldwide^[20]. However, a recent report from Europe indicated an even higher prevalence of CD at 322 per 100,000 population^[21].

In contrast, in less developed areas, despite that fact that the prevalence of disease is rapidly increasing, the overall prevalence rate remains much lower than in Western countries^[22]. The prevalence of CD in Japan is 21.2 per 100,000 individuals^[23] and in Korea the prevalence was 11.2 per 100,000 inhabitants in the period between 2001 and 2005^[24]. Of interest Lebanon's prevalence rate falls between developed and developing countries with a rate of 53.1 per 100,000 population in 2007^[25].

ETHNICITY, AGE AND GENDER

In terms of ethnic and racial distribution, CD was generally considered to be a disease of Caucasians^[26] and Jewish ethnic groups^[27] whereas Hispanics and Asians were less affected^[28]. However, recent reports indicate that the disease is rapidly increasing among Asians^[29], and especially in families migrating from Asia to the West^[30]. On the other hand, the disease is reported less commonly in the indigenous populations resident in Canada, Australia and New Zealand^[17].

Overall most cases of CD are diagnosed between the ages of 15 to

35 years^[18]. However, CD can present through the whole age range, from infancy to the elderly. For example, many cases are seen in preschool children^[31] and there is a second peak in diagnosis observed around 60 years of age^[26]. Overall, the disease remains most common among the most productive section of community with 80 % of cases aged less than 40 years^[32].

In terms of gender distribution, CD is slightly more common in females than males, with a female: male ratio of around 1.3: 1^[33]. In younger age groups, however, the ratio is reversed with a slight predominance of boys compared to girls^[33].

RECENT TRENDS OF EPIDEMIOLOGICAL DATA

The rapid increase in incidence and prevalence of CD worldwide has been especially prominent in Asian countries^[34]. In one district of South Korea the incidence rate of CD rose significantly from 0.5 to 1.34 per 100,000 of the population over a 20 year period^[35]. A meta-analysis reviewing descriptive data of CD (1950 to 2007) in one mainland city in China, reported the disease is no longer uncommon in that country, with the incidence increasing annually by 0.848 and 2.29 for the prevalence a year (per 100,000 individuals respectively)^[22]. In Hong Kong, a hospital based cohort study reported an increase in incidence from 0.4 to 1 per 100,000 between 1990 and 2001^[29]. Likewise, data from Singapore has shown that the prevalence of CD has risen from 1.3 cases to 7.2 cases per 100,000 inhabitants^[36].

Moreover, areas that have previously reported incidence rates amongst the highest in the literature are still experiencing a continuous growth in the number of people diagnosed with CD. Denmark and Sweden have shown a rapid increase in the incidence rates of CD, rising from 4.1 per 100,000 in 1980 to 8.6 per 100,000 in 2005^[9]. In Wales (Cardiff) the incidence increased from 5.5 in between 1986-1990 to 6.6 per 100,000 in between 1996-2005^[19]. In the USA the incidence rate of CD has almost doubled in the period in between 1991 to 2002^[37]. Moreover, recent reports from Australasian studies also indicate an increase in rates of CD^[17]. In Israel, where CD rates are already considered high, a rapid rise in rates of the disease has also been described^[38]. The prevalence of CD has increased by more than 4-fold over a 20-year period between 1987-2007 in the kibbutz settlements in Israel^[39]. A similar trend was also reported in another study of adolescent Jewish Israelites, where the prevalence doubled over the 13 year period of study^[40].

Paediatric reports have been prominent in documenting increasing rates of CD in conjunction with a reduction in median age at diagnosis^[41,42]. In a report involving paediatric based population studies based in eight different countries including USA, Canada, Spain and Ireland with a total of nine provinces, there was an increase in paediatric CD in the period between 1990 and 2010^[43]. A similar trend was seen in France, where the incidence among paediatric patients increased from 3.5/100,000 in 1990 to 5.2/100,000 in 2005^[19]. Large changes have also been demonstrated in Australian children in recent years^[17]. Phavichitr *et al*^[44] in a retrospective study of CD amongst Australian children in the state of Victoria, reported that incidence of paediatric CD had increased almost 10 fold over 3 decades.

Migrant studies have also revealed dramatically increasing incidence and prevalence of CD in migrant populations, most notably in the paediatric population, moving from developing to developed countries. A Canadian study of the IBD paediatric population of British Columbia found that the incidence of IBD, including CD, was significantly higher in children of South Asian descent compared

with non-South Asian IBD patients^[45]. A Swedish cohort study also investigated the risk of developing IBD among immigrants and revealed a significant rise in the incidence of CD in second generation migrant groups originating from developing countries (such as Iraq)^[46]. A similar conclusion was reached by Naidoo *et al.*^[47] in a study of IBD behavior among Australian children of Middle Eastern descent. The authors found a higher prevalence of IBD (including CD) among children with Middle East ancestry compared to a non-Middle Eastern control group^[47].

It should be considered that increased awareness of health professionals and the public to the disease may have contributed to the reported increasing incidence and prevalence of the disease^[34]. Nevertheless, there is significant evidence indicating that there is a true rise in the incidence and prevalence of CD throughout the world^[9,41,48].

ROLE OF ENVIRONMENTAL FACTORS IN CD PATHOGENESIS AND CHANGING EPIDEMIOLOGY

Although the precise aetiology of CD, as well as the forces behind the changing epidemiology, remain unknown, most hypotheses propose that environmental factors are the predominant contributing force in the rise of CD rates and earlier disease onset^[19,49,50]. The changing diet habits of Asian populations is one factor that may be responsible for the rising incidence^[34,51]. A multicentre case-control study in Japan found that a higher consumption of refined sugars and a high fat diet correlated with the increase in newly diagnosed cases of CD in that country^[52]. Similarly, a Canadian case-control study involving 130 patients with newly diagnosed CD, revealed that the consumption of fruits, vegetables and dietary fibres protected against CD, whereas high intake of fats was linked with an increased risk^[53].

Perinatal and postnatal factors including the type of feeding and early life exposure to drugs, antibiotics and vaccines have been also suggested to be associated with the increase in immune-related diseases including IBD^[54]. These factors are largely involved in mucosal homeostasis through influencing the initial colonization of the gut and the microbial balance in early life^[55]. Recently, a population based case-control study in the Asia-Pacific region (including eight Asian countries and Australia), highlighted the critical role of early life factors and most notably breast feeding, in modulating the subsequent risk of developing CD^[56]. However, two large prospective cohorts studies from the USA also looked at the influence of early risk factors in developing CD and did not find any correlation between these risk factors and later disease in adults^[57].

The hygiene hypothesis is another environmental factor suggested to contribute to the burgeoning prevalence of many inflammatory disorders including CD. This theory identifies that environmental changes such as better housing, better nutrition, improved hygiene, better living standards and sanitation have led to a rapid decline in infectious disease resulting in a weakening and/or under-development of the immune response to pathogens in early life^[58,59]. The weakened and/or under-developed immune response and altered intestinal microbial community leaves the individual more vulnerable to developing immunological diseases, including CD, later in life^[54].

In addition to the previously discussed environmental factors, there is a correlation between CD and other environmental exposures including smoking and appendectomy. Reports show that while smoking may be protective against ulcerative colitis (another form of IBD), it is a risk factor for developing CD^[59]. Furthermore, there is a

clear relationship between smoking and disease severity^[60]. Similarly, appendectomy appears to be a strong risk factor for the development of CD^[61].

CONCLUSIONS

CD is a chronic and incurable inflammatory disease predominantly affecting adults, although recent reports show increasing numbers of diagnoses among children. CD is more common in people with Caucasian and Jewish ethnic backgrounds, but is becoming increasingly prevalent in Asian populations. Originally considered a disease solely of Western societies, studies now show that CD is an emerging disease throughout the world including less developed countries, most notably in Asia. Changing diet habits, including Westernization of the diet, appear to be a major environmental factor contributing to the changing epidemiological patterns of CD. However, perinatal and early life events, which influence the development of the intestinal microflora and the immune system, and changes in living standards, may also contribute.

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CONFLICT OF INTERESTS

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Peer reviewer: Ulrich Böcker, MD, Professor (eo.), Department of Medicine IV, Gastroenterology and Diabetology, Vivantes Klinikum Neukölln, Rudower Straße 48, D-12351 Berlin, Germany.