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INFLAMMATORY BOWEL DISEASE IN HISPANIC COMMUNITIES: a concerted South American approach could identify the aetiology of Crohn's disease and ulcerative colitis

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ABSTRACT - Despite intensive research we remain ignorant of the cause of both Crohn's disease and ulcerative colitis. The dramatic rise in incidence, particularly of Crohn's disease, points towards environmental factors as playing a significant role. A major purpose of this review is to stimulate a co-ordinated international effort to establish an on-going data base in Central and South America in which new cases are registered and through which investigations into aetiology can be conducted. In both Brazil and Mexico there is evidence that the incidence of ulcerative colitis is increasing, as also is the case for Crohn's disease in Brazil. The pattern of disease is, therefore, directly comparable to that reported from Europe and the USA during the 1970s and 1980s, but much lower than contemporary data from Spain. Although the incidence is similar to that reported from Portugal, the studies from Almada and Braga were conducted a decade before that from Sao Paulo. The situation in Brazil compares dramatically with Uruguay and Argentina where the reported incidence of inflammatory bowel disease is significantly less. However, with growing industrialisation it is likely that there will be an explosion of inflammatory bowel disease in some areas of Central and South America over the next 20 years. The creation of a network of researchers across South and Central America is a real possibility and through a Concerted Action there is the possibility that major strides could be made towards understanding the cause of inflammatory bowel disease and so develop preventive strategies.

HEADINGS - Inflammatory bowel diseases. Crohn disease. Proctocolitis. Ulcerative colitis. Database.

INTRODUCTION

Interest in the epidemiology and aetiology of inflammatory bowel disease has been a central theme in gastroenterology for a long time. One hundred years ago Kennedy Dalziel was amongst the earliest clinicians to describe what later became known as Crohn's disease. At the time he wrote: "I can only regret that the aetiology of the condition remains in obscurity, but I trust that 'ere long further consideration will clear up the difficulty"[16].

However, despite intensive research on all fronts we remain ignorant of the cause of both conditions with many theories coming into fashion only to be later dismissed. The dramatic rise in incidence, particularly of Crohn's disease, points towards environmental factors as playing a significant role. Further support for such a view comes from the spread of the disease into Southern and Eastern Europe and now India and China. In 1985 following reviews of the epidemiology of ulcerative colitis[31], Crohn's disease[33] and a study of mortality[17] it was suggested that: "Particular attention in the future will focus on such countries as Spain and Portugal; Central and South America are of interest for similar reasons"[31].

This review cites more than 20 studies that have subsequently come from Spain and Portugal (Table 1 and Figure 1). A major drive to this work was the Concerted Action funded by the European Union during the 1990s[19]. It was a descriptive study of the incidence of inflammatory bowel disease in Northern and Southern Europe. It achieved this through standardisation of definitions of disease[32] and of the methodologies used to identify candidate cases and separate them into confirmed cases and non-cases[7]. Additional benefits that arose from the program included:

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TABLE 1. Incidence studies of inflammatory bowel disease from Spain and Portugal

	Years	Ulcerative colitis	Crohn's disease
Spain			
Navalmoral de la Mata[2]	2000 - 2009	9.8	5.9
Madrid[26, 27, 44]	1998 - 2003	6.2	7.1
	1983 - 1988	2.4	1.3
Navarra[5]	2001 - 2003	10.3	6
Pamplona[4]	1983 - 1993	3.8	2.5
Huelva[20]	1996 - 2003	5.2	6.6
Asturia[27, 42, 43]	1994 - 1997	9.5	6
Aragon[25]	1992 - 1995	7.2	3.9
Castellon[35]	1992 - 1996	6.8	1.9
Sabadell[10]	1991 - 1993	9.8	5.2
Vigo[10]	1991 - 1993	7.7	5
Mallorca[10]	1991 - 1993	7.8	5.8
Motril[10]	1991 - 1993	4.3	6.5
Marbella[39]	2000 - 2001	7.3	
Granada[28]	1979 - 1988	2	0.9
Soria[1]	1981 - 1990	3.2	1.3
Galicia[40]	1976 - 1982	0	0.8
Sagunto[21]	1983 - 1989	4	3.1
Mérida[38]	1996 - 2000	5.1	2.2
Portugal			
Almada[45]	1991 - 1993	1.7	2.3
Braga[45]	1991 - 1993	5.5	3.7

The incidence data from published papers is recorded as cases/100,000 population/year

FIGURE 1. Distribution of inflammatory bowel disease in Hispanic Communities.
Incidence data is quoted for ulcerative colitis and then Crohn's disease. In the case of Madrid the most recent figures are quoted first.

- The creation of networks of research teams in Europe;
- Promotion of national financing of research projects relevant to European priorities in health research;
- Transfer of expertise from centres of excellence to less advanced research teams[19].

However, by the 1990s the incidence of ulcerative colitis had dramatically increased in Spain and this change was to be followed shortly by similar increases in the frequency of Crohn's disease (Table 1)[15]. A Concerted Action 10 years earlier would have allowed more direct observation and assessment of those factors which are responsible for the worldwide expansion of these conditions. Such changes have now been reported in China, India and many other communities. Central and South America are the last major regions where inflammatory bowel disease is still uncommon and in which there is hope that the aetiology of these conditions might be identified through basic epidemiological research. A major purpose of this review is to stimulate a co-ordinated international effort to establish an on-going data base in Central and South America in which new cases are registered and through which investigations into aetiology can be conducted. It also presents a unique opportunity to investigate cohorts and the subsequent occurrence of Crohn's disease or ulcerative colitis. For example, young people who are recruited for military service are, in general, healthy and basic data on demography, social habits and family history can be recorded. Such a cohort can be followed long-term and this form of approach has been adopted in Korea, which is another low incidence area[23]. Retrospective studies using military cohorts have been used in the USA, but this lacks the rigour of a prospective approach[37]. The Millenium Cohort Study will address some of these issues[41]. It uses traditional and web based methods to follow almost 100,000 service personnel and such an approach could be adopted in Central and South America.

Incidence and prevalence in Central and South America

Almost without exception ulcerative colitis is commoner than Crohn's disease and this is true in studies from Brazil, Uruguay and Puerto Rico (Table 2)[3, 11, 49, 50]. In both

TABLE 2. Incidence studies on inflammatory bowel disease in Latin America

	Period	Ulcerative colitis	Crohn's disease	Unclassified
Brazil[50]	2001 - 2005	4.5	3.5	1.8
	1996 - 2000	6.8	1.5	0.4
	1991 - 1995	3.9	0.7	
	1986 - 1990	0.7	0.2	
Panama[24]	1987 - 1993	1.2	0	
Argentina[24]	1987 - 1993	2.2	0	
Peru[12]	2001 - 2003	2.1		
Uruguay[11]	2007 - 2008	4.3	0.8	
Mexico[8]	2004	2.3		
	2008	4.1		
Puerto Rico[3]	1996 - 2000	3.3	2	2.5

The incidence data from published papers is recorded as cases/100,000 population/year

Brazil[47, 50] and Mexico[8] there is evidence that the incidence is increasing, as also is the case for Crohn's disease in Brazil (Table 2)[50]. The pattern of disease is, therefore, directly comparable to that reported from Europe and the USA during the 1970s and 1980s and more recently from Eastern Europe and China. However, the incidences are significantly lower than contemporary data from Spain. (Figure 1). In general, they are similar to those from Portugal but the studies from Almada and Braga were conducted a decade before that from Sao Paulo[45, 50].

The situation in Brazil[47, 50] compares dramatically with Uruguay and Argentina[11, 24] where the reported incidence of inflammatory bowel disease is significantly less. Such variations between adjacent countries would give particular value to a continental study of inflammatory bowel disease, provided it adopted a more analytical style than the simple descriptive approach taken by the Concerted Action in Europe. Work in Uruguay would strongly support the view that such differences are real and not due to variations in the way cases were identified[11]. Clearly the very existence of such differences between countries should be a major stimulus to international co-operative studies in Central and South America.

Most patients in the Brazilian study were urban dwellers and of European descent[50]. The urban predominance of inflammatory bowel disease has been described in a number of studies[18, 29, 34, 46]. It seems to be a particular feature early in the appearance of the condition in a community with the difference lessening and ultimately disappearing with time. It is of interest that the Brazilian study links the movement of people into urban areas with economic driving factors including the need for women to work in factories and other industries so exposing them to environmental factors which may play a part in the aetiology of inflammatory bowel disease.

The flow of immigrants into Argentina, Uruguay, Brazil and Venezuela also provides opportunity for further assessments[22]. Such work was done on the occurrence of cancer in migrants in the 1990s in Uruguay[48], Brazil[9] and Argentina[30]. An interesting recent Spanish study on emigration looked at 34 patients who had emigrated to other parts of Europe and 16 to South America[6]. The authors suggested that emigration was associated with ulcerative colitis and not with Crohn's disease. It also linked emigration to industrialised European countries and not to Latin America during the first decade of the 21st Century. Work in the UK has demonstrated that the incidence of colitis can rise to that of the host population and even exceed it within one generation[14]. With growing industrialisation it is likely that there will be an explosion of inflammatory bowel disease in some areas of Central and South America over the next 20 years.

CONCLUSION

What is the way forward? The main impact of the Concerted Action on inflammatory bowel disease in Europe was to create an atmosphere in which multi-national studies became a real possibility. Clinicians with an interest in inflammatory bowel disease from a range of countries came together and worked out common agendas for research and shared their methods and pooled results. Into these groups they drew statisticians and patient representatives. Such activities helped stimulate the emergence of organisations such as the European Crohn's and Colitis Organisation (ECCO)[13]. The creation of a network of researchers across South and Central America is a real possibility. There already exist registers of patients with inflammatory bowel disease in a number of countries e.g. Brazil[47, 50], Argentina[24], Panama[24], Uruguay[11], and Puerto Rico[49]. The maintenance of such registers can be costly and requires dedicated staff. Registration on computer data bases and sharing of data can be restricted by legislation related to privacy and by concerns about the availability of such data outside national boundaries. However, such difficulties can be overcome and by pooling data the results become more robust and such studies may be the last opportunity to readily identify those environmental factors which are likely to be a significant factor in the emergence and spread of inflammatory bowel disease across the world.

Patient self help groups can provide useful support to any network of researchers through explanations to members and, at times, political lobbying. Such groups already exist in Brazil and Argentina. They tend to appeal to a certain sector of the population e.g in the UK membership is dominated by English women and a significant number of people do not join because they do not wish to "broadcast their illness"[36]. Nevertheless the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) has emerged as a significant umbrella organisation which supports patients and clinicians. It recently welcomed Fundación Mas Vida de Crohn & Colitis Ulcerosa from Argentina as an associate member.

The development of these networks, the facilitation of meetings and support of a research program with common protocols and clearly defined endpoints, which will include measures of incidence and an investigation of potential aetiological factors, will require funding. In days when such funds are hard to achieve the role of pharma companies should not be dismissed. South America is likely to be a major market for 5ASA compounds and for biologic therapies. It is not unreasonable to expect them to provide seeding funds to, at least, initiate an international meeting of clinicians in Central and South America so that a "Concerted Action" on the epidemiology and aetiology of inflammatory bowel disease can happen.

Farrukh A, Mayberry JF. Doença inflamatória intestinal nas comunidades Hispânicas: uma orquestrada abordagem Sul-Americana poderia identificar a etiologia da doença de Crohn e da retocolite ulcerativa. Arq Gastroenterol. 2014,51(4):271-5.

RESUMO - Apesar da pesquisa intensa, ainda permanecemos ignorantes quanto à causa da doença de Crohn e da retocolite ulcerativa. O aumento dramático da incidência, particularmente da doença de Crohn, aponta para fatores ambientais desempenhando um papel significativo. Um grande propósito desta revisão é estimular um esforço internacional coordenado para estabelecer uma base de dados em curso na América Central e do Sul, na qual novos casos são registrados e através dos quais investigações sobre a etiologia seriam realizadas. No Brasil e no México, há evidências de que a incidência da colite ulcerosa está aumentando, como também é o caso da doença de Crohn no Brasil. O padrão da doença é, portanto, diretamente comparável àquela relatada da Europa e dos Estados Unidos durante a década de 1970 e 1980, mas muito mais baixa do que dados contemporâneos da Espanha. Embora a incidência seja semelhante à relatada a partir de Portugal, os estudos de Almada e Braga ocorreram uma década antes do que em São Paulo. A situação no Brasil compara-se dramaticamente com Uruguai e Argentina, onde a incidência relatada de doença inflamatória intestinal é significativamente menor. No entanto, com a crescente industrialização é provável que haja uma explosão de doença inflamatória intestinal em algumas áreas da América Central e do Sul nos próximos 20 anos. A criação de uma rede de pesquisadores em toda a América Central e do Sul é uma possibilidade real e, através de uma ação articulada, há a possibilidade de que grandes avanços poderiam ser feitos no sentido de compreender a causa da doença inflamatória intestinal e então desenvolverem-se estratégias preventivas.

DESCRITORES - Doenças inflamatórias intestinais. Doença de Crohn. Proctocolite. Colite ulcerativa. Base de dados.

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