Epidemiology of Ulcerative Colitis in South Asia

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The South Asian region comprising of India, Pakistan, Bangladesh, Nepal, and Sri Lanka is multi-ethnic with vast cultural differences. Yet they have in common, a strong predisposition for inflammatory bowel disease especially ulcerative colitis (UC). The vast majority of the population is rural with limited access to health care facilities. Community based studies on epidemiology of UC are sparse making it difficult to extrapolate data for the whole region. India has the highest incidence and prevalence of UC in Asia which is higher than the published figures for Korea and Japan, the two leading industrialized countries in Asia. Asian diaspora studies have revealed an unmasking of the disease when natives of this region migrate to countries with a higher prevalence of the disease. Data mainly from the UK suggests a higher incidence of the disease in Asian migrants compared to the indigenous population. Incidence data from within the sub-continent suggests a higher incidence of the disease in India as compared to its southern neighbour Sri Lanka suggesting a north-south gradient. Time trend studies from India do not suggest an increasing incidence of disease as has been observed in other parts of Asia. Some data point to phenotypically different disease in south Asian patients as compared to Caucasians. Familial clustering and cumulative colectomy rates are higher in Western patients as compared to their Asian counterparts. Asian patients with UC have a significantly lower risk of development of colorectal carcinoma vis a vis the Caucasian population. There is a pressing need for more studies on the epidemiology, long-term outcome and natural history of the disease in this region. (Intest Res 2013;11:250-255)

Key Words: Inflammatory bowel disease; Ulcerative colitis; Epidemiology; Incidence; Prevalance

INTRODUCTION

Asia is perhaps the most diverse continent in terms of ethnicity, cultural variation, socio-economic status and health care facilities. Whereas Japan, South Korea, and Singapore have excellent health care facilities and health data bases at par with Europe and North America, many countries especially in South Asia (Afghanistan, Myanmar, Nepal, etc.) lack even basic health care facilities in most areas; therefore any comparison of disease epidemiology in Asia versus North America or Europe is not only difficult but is likely to be erroneous because of paucity of reliable data. This review deals with epidemiology of IBD in South Asia with a focus on the Indian subcontinent which includes published data from Pakistan, Bangladesh and Sri Lanka in addition to India. The population of the Indian sub-continent is not uniform unlike Japan, China, or Korea as it is a mixture of Caucasian population in the northern part, Mongoloid in the Eastern region and Dravidian in the Southern part of the region. To understand the variability of IBD in India amongst different ethnic and cultural groups, it is better to view it as a small continent rather than a large country. A unique feature of the sub-continent has been the large scale migration of population which occurred from the northern and eastern parts of the sub-continent to Britain and subsequently North America shortly after the end of the Second World War. Today, Britain, Canada, and USA have a sizeable migrant population from India, Bangladesh, and Pakistan. Disease in the migrant population in these countries has given considerable insight into the epidemiology of the group of diseases referred collectively to as IBD.

IBD is a chronic inflammatory disease of the intestines in genetically predisposed individuals associated with well defined extra-intestinal complications with spontaneous remission and relapse in the natural course of the disease. The pathophysiology involves an aberrant immune response...
to the gut microbiota.\textsuperscript{1} Whereas the disease is limited to the colon in UC; CD can involve any part of the intestinal tract from the oral cavity to the anus. UC is characterized by mucosal inflammation, whereas transmural involvement is an integral feature of CD. The disease was initially thought to be uncommon in South Asia where bloody diarrhea was attributed mainly to infective pathogens. Recent population based and referral center cohorts have however suggested a rising incidence and prevalence of non-infective diseases in Asia which has been attributed to the rapid industrialization and westernization of this region. Incidence data from Asian populations have been derived mostly from hospital based cohorts with the exception of population based data from Japan, India, and Korea.\textsuperscript{2}

UC was first reported from India in the late 1930s when it was still a British colony; however, it was only in the late 1960s that there was a flurry of reports suggesting the existence of the disease in the northern and western parts of the country.\textsuperscript{3-5} Since then, there have been only two studies which have been specifically designed to determine the incidence and prevalence of the disease in India. Unfortunately both these studies have been conducted in the northern part of the country albeit with an interval of 17 years and hence the hospital data may not be reflective of the whole country.\textsuperscript{6,7} More recently a task force carried out an epidemiological study in Rohtak district of Haryana in 1986 and noted a prevalence rate of 42.8/100,000.\textsuperscript{8} Since then, there have been only two studies which have been specifically designed to determine the incidence and prevalence of the disease in India. Unfortunately both these studies have been conducted in the northern part of the country albeit with an interval of 17 years and hence the hospital data may not be reflective of the whole country.\textsuperscript{6,7} More recently a task force set up by the Indian Society of Gastroenterology (ISG) collated data from five zones of the country to survey the epidemiologic and clinical features of IBD in India.\textsuperscript{9} Since the task force data was essentially derived from a questionnaire based proforma filled by practicing gastroenterologists, the information derived from it cannot be as robust as that obtained from a population based study. Similarly the sole prevalence study of IBD from Sri Lanka is a hospital based study from only two districts of the country.\textsuperscript{10} These introductory statements underscore the need for more population based studies from different parts of the sub-continent.

**MAIN DISCOURSE**

1. **Prevalence and Incidence of Ulcerative Colitis in South Asia**

Two issues merit discussion on this epidemiologic feature: first the prevalence and incidence of UC in India and secondly the question of rising incidence of the disease as has been reported from other Asian countries. Two studies from the northern part of the country performed at an interval of 17 years estimated the prevalence of the disease in the narrow range between 42.8 and 44.3 per 10,000 population. Khosla et al.\textsuperscript{9} carried out an epidemiological study in Rohtak district of Haryana in 1986 and noted a prevalence rate of 42.8/100,000. Sood et al.\textsuperscript{2} screened a population of 51,910 comprising both rural and urban areas in Ludhiana through a cluster sampling method and detected 23 patients with UC giving a prevalence rate of 44.3/10,000; 3 new cases were identified after a second visit 1 year later to give a crude incidence rate of 6.02/100,000 person-years. The limitation of both these studies was that they were undertaken in the same geographical region where the population is predominantly Punjabi or Sikh. Studies on epidemiology of IBD done on the Indian diaspora in Britain have clearly shown that Sikhs have a higher incidence (16.5/100,000 person-years) vis a vis other ethnic/religious groups such as Hindu (10.8/100,000 person-years) or Muslim (1.8/100,000 person-years).\textsuperscript{11-13} Hence the prevalence figures obtained in these studies may not be a true reflection of the disease burden of the whole country. Niriella et al.\textsuperscript{14} determined the incidence of UC in Sri Lanka to be 0.69/100,000 person-years. The limitation with their study as with several other studies from Asia was that it was a hospital based study. Epidemiological studies from developed countries have highlighted the fact that hospital based studies tend to underestimate the disease burden as compared to population based studies. In light of this fact, it is not surprising that the incidence of the disease in Sri Lanka is nearly ten fold lower than in India despite the geographical proximity of the two countries. Apart from this there is scanty data to document a North-South gradient of the disease as has been observed in Europe.

Compared to India, the incidence of the disease is much lower in other Asian countries where it ranges from 0.68-5.40/100,000 person-years.\textsuperscript{2} Amongst the Asian countries, Japan and Korea have the highest incidence of UC after India. Several studies conducted between 1988 and 2005 in Japan estimate the disease incidence to be between 0.02-1.95/100,000 person-years.\textsuperscript{15-17} The corresponding range for Korea is 0.34-5.40/100,000 person-years.\textsuperscript{18} The Korean data is based on population based studies whereas the Japanese data is derived from both hospital based data and disease registry.

Time trend studies from several Asian countries suggest a rising incidence of IBD. The 30-year period from 1961-1991 showed a near hundred fold increase from 0.02/100,000 in 1961 to 1.95/100,000 person-years in 1991 in Japan.\textsuperscript{2} Korean data showed a greater than tenfold increase in the incidence of UC from 0.34-5.40/100,000 over a period of more than 2 decades from 1986 to 2008. This increase in incidence over a relatively short period of time strongly suggests that environmental factors such as industrialization and westernized lifestyle may play a significant role as Koreans have maintained a high level of genetic homogeneity. On the contrary, data from India though sparse has shown a near constant prevalence rate of 42-44/100,000 over a period of two decades from 1984 to 2003.\textsuperscript{8} These observations argue against the predominant role of environmental factors in the pathogenesis of UC in South Asia and suggest that genetic factors (Caucasian race) play a more important role than environmental factors in the causation of UC.
2. What Do the Diaspora Studies Tell Us?

Asian diaspora studies provide a unique insight into the epidemiology of IBD. The latter part of the 21st century witnessed large scale migration from the Indian subcontinent to the UK and North America. The dominant migrant groups were from Punjab (both Indian and Pakistani) and Bangladesh (erstwhile East Pakistan). The initial studies highlighting the higher genetic predisposition of Hindus and Sikhs for IBD came from the British Midlands in the early 1990s. Subsequently reports from Canada have reconfirmed the observations of the earlier studies from Leicestershire. The incidence and prevalence of UC amongst the South Asian migrants is considerably higher in their adopted countries as compared to their country of origin. Interestingly, data from Leicestershire showed a higher incidence and prevalence of UC in South Asians versus the Caucasian population of the same geographical area. The time trends suggest that the incidence of UC has been steadily rising among Asian migrants from 1981-1994. Probert et al. documented the incidence and prevalence of UC in South Asians to be 13.9/100,000 person-years and 172.5 respectively in the period between 1981-1989. In the period between 1991-1994 the incidence increased from 13.9 to 17.2 in the same geographical region. These figures are much higher than the published reports from India where the incidence rate UC is only 6/100,000 person-years and the prevalence is in the range of 42-44/100,000 person-years. As pointed out earlier, the epidemiological studies done in India were from the northern part of the country where the dominant ethnic group are the Punjabis and Sikhs as seen in Leicestershire. Studies from the same region (Midlands) have also displayed that the disease pattern of UC in the second generation of immigrants follows that of the indigenous population. Similar high incidence rate of UC has also been documented in Bangladeshi population albeit at a somewhat lower rate than seen in North Indian migrants suggesting that the whole Indian sub-continent tends to show the phenomenon of unmasking of the disease after migration to countries of higher prevalence. The caveat to the statement is that there is a dearth of well-designed epidemiological studies with a large sample size from all south Asian countries.

3. Is the Disease Phenotypically Different in Asia?

Despite the fact that the basic disease pathology is no different in Asia versus the West there may be some variations in the clinical presentation between the two regions. The differences pertain to familial clustering, presence of extra-intestinal manifestations (EIM), severity and long term outcome. Asian data on these aspects is sparse and none of the studies available have been designed to address these specific issues. Even the recently published Indian Society of Gastroenterology consensus statement on UC does not have hard data on the need for surgery and long-term outcome in these patients.

Some data suggests that familial clustering is uncommon in Indian/Asian patients with UC. In Asia a positive family history of UC in first degree relatives has been reported to be in the range of 0.6-8.0% whereas the corresponding figures from the West are in the range of 14.6-29.4%.

The decreased familial clustering is evident even in South Asian migrants to the UK which as a group has a higher incidence and prevalence of the disease as compared to the indigenous Caucasian population. The ISG-IBD task force data has similarly documented that a positive family history is obtained in only 2.3% of Indian patients with UC. Unpublished data from our department documented the presence of UC in only four first degree family members of 104 (3.8%) patients. The reasons for this disparity between the East and the West are as yet unknown.

Data on the presence of EIM of UC in Indians is paradoxically high and hence controversial. The recently published ISG consensus statement on UC has reported that nearly 50% of patients with UC had extra-intestinal symptoms, principally arthralgia, backache, ocular and skin lesions. Of the three published studies on this aspect from India, both Kochhar et al. and Habeeb et al. documented the presence of EIM in excess of 30% whereas Pokharna et al. found EIM in only 6% of their patients. This wide disparity can be explained by the laxity of the disease defining criteria especially with reference to arthralgias. It needs to be emphasized that arthritis should be documented as an EIM whereas the inclusion of arthralgia or back-ache, both of which are quite common in the general population would result in a spurious inflation of this manifestation. The wide disparity of arthritis as an EIM is not unique to India as a recent Iranian review has also reported that occurrence of arthritis ranged between 3.5-32.0%.

The presence of ocular manifestations in all the three studies from India was in the narrow range of 4-8%. A low frequency of EIM ranging between 6.1-9.5% has also been reported from China and Sri Lanka. In contrast arthropathy both pauci-articular and polyarticular has been reported in ≤5% of patients with UC from the West. Until uniform diagnostic criteria are used, there is likely to be a wide variation in the prevalence of EIM in UC in different parts of the world.

It has been suggested that Asian patients have milder disease vis a vis the developed world. This pertains to both the extent of the disease as well as disease severity. Immigrant studies from Britain certainly do not support this statement. Disease extent of UC in the UK born children of South Asian immigrants is comparable to that of the European population. Walker et al. reported that 63% of South Asian patients with UC had pancolitis compared with 42.5% of the indigenous European population (P<0.0001). In the Indian task force data, 18%, 38%, and 42% of 724 patients with UC had proctitis, left sided disease and pancolitis respectively. Pancolitis has been documented in 7-45% from various countries.
across Asia.\textsuperscript{30} The wide variation of pancolitis may also be attributed to the referral bias, as studies from tertiary referral centers are more likely to have a higher proportion of patients with pancolitis. As a corollary to the above statement, epidemiological studies are bound to have a higher proportion of milder cases vis a vis hospital-based surveys. This point is elaborately illustrated by the fact that pancolitis comprised only 16\% of the cases of the epidemiological study by Sood et al.\textsuperscript{3} whereas the Indian Society of Gastroenterology task force data based on collated data from gastroenterologists estimated this figure to be 42\%.\textsuperscript{8}

There are some data to suggest that colectomy in UC rates are lower in Asia as compared to the West. Studies from the West have reported cumulative colectomy rates at one year of 6-11\%, 5 years of 20\% and 10 years of 24-28\%.\textsuperscript{2,32} Hilmi et al.\textsuperscript{32} reported the corresponding rates of 3.4\%, 5.9\%, and 15.6\% for the same intervals. As elegantly discussed by Prideaux et al.\textsuperscript{2} the lower rates in Asian patients could be multifactorial: milder disease course, variations in disease management or different thresholds for surgery in Asia.

4. Colorectal Cancer (CRC) in South Asian Patients with Ulcerative Colitis

CRC is a well-recognized complication of long-standing UC. There is a wide variation in the development of CRC in Asian patients with UC. Incidence and prevalence of sporadic CRC unrelated to UC in South Asia is amongst the lowest in the world. This is mainly attributed to the low consumption of red meat coupled with a largely vegetarian diet in many parts of South Asia. Asian data from the KASID study\textsuperscript{33} revealed an overall prevalence of CRC in UC to be 0.37\%. The cumulative risk of CRC in UC at 10 years, 20 years and 30 years was 0.7\%, 7.9\%, and 33.2\%,\textsuperscript{31} The mean age at the time of diagnosis was 49.6 years and the mean duration of UC prior to the development of the CRC was 11.5 years. These data are comparable to the data from the West. In contrast several studies from India, China, Malaysia and Sri Lanka suggest a lower risk of development of CRC in the setting of UC as compared to the West.\textsuperscript{2,3,34,35} Venkataraman et al.\textsuperscript{35} reported that in those with a disease duration of 10-20 years, the incidence density was 2.34/1,000,000 person-years duration (PYD) for all patients with colitis and 4.5 PYD for patients with pancolitis. For those with disease duration greater than 20 years, the incidence density was 2.73/1,000,000 PYD for all patients and 4.9/1,000 PYD for patients with pancolitis. Duration of disease greater than 10 years and extent of disease were the only risk factors significantly associated with CRC. Thus based on limited data, the conclusion may be drawn that the risk of development of CRC in UC in South Asia is considerably less than that in the West and some parts of Far East Asia.\textsuperscript{35}

5. Current Lacunae in Literature

The south Asian sub-continent comprises of India, Pakistan, Bangladesh, Nepal, and Sri Lanka. As per the 2001 population census, 72\% of the Indian population of 1.2 billion lives in 638,000 villages where health care facilities are grossly deficient. The same distribution of population probably holds true for other countries of this region as well. As of date there have been only two community based studies from the northern part of the country which have addressed the issue of epidemiology of UC.\textsuperscript{6,7} Whether data from these largely urban studies can be extrapolated to the whole country or sub-continent is a moot point. More studies are needed from other parts of the region to validate the earlier studies and also to address the issue of rising incidence of IBD in Asia. The dichotomy of the population into rural and urban groups with widely different living conditions and dietary habits offers a unique opportunity to study the role of environmental factors and urbanization in the causation of the disease. Cohort studies describing the natural history of the disease especially with reference to the need of surgical therapy have yet to be undertaken despite the recognition of the disease in India for more than five decades. Studies to identify putative risk factors for the disease in this region are also lacking; it is unlikely that appendectomy and oral contraceptive usage have any role in the causation of disease in this region considering that their prevalence in this region is negligible. The onus for conducting these studies must largely be on government health organizations like the Indian Council of Medical Research (ICMR) in India so that data from all parts of the country may be collated. Alternatively these could also be done by national societies dedicated to gastrointestinal diseases which exist in most countries. ISG has already set up various task forces to provide practice guidelines for several gastrointestinal diseases.

CONCLUSIONS

South Asia has seen a paradigm shift in the spectrum of disease over the past 3-4 decades. The focus has shifted from infectious disease in the past to non-infectious and lifestyle disorders as are prevalent in the developed countries. This is true not only for metabolic and cardiovascular disease but also for intestinal diseases like IBD and celiac disease. The changing patterns in the geographical distribution of IBD with increasing number of cases in parts of the world where these diseases used to be rare implies that environmental factors such as diet and urbanization may play important roles in the development of these diseases.\textsuperscript{35} As suggested by Prideaux et al.\textsuperscript{2} lifestyle changes in Asia in the last 2 decades have resulted in a more westernized lifestyle which implies a move away from the traditional fiber rich foods to a diet rich in refined sugars, fats and animal protein. Current data suggests that India has the highest incidence and prevalence of
UC in Asia, even more than Japan and Korea which are the most industrialized and westernized nations of this region. India with a population of approximately 1.2 billion and a high growth rate is likely to have a huge disease burden of IBD in the future. With this background data it is not improper to state that India is likely to be the IBD capital of Asia. The high cost of second line drugs coupled with the need for lifelong therapy for some of these medications is going to have a direct impact on the health care economics of the country. The increasing disease burden will, however hopefully lead to availability and development of more specialized centers to treat patients with IBD and its associated complications.

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