Symposium : Gastroenterology & Hepatology

Epidemiology of Inflammatory Bowel Diseases in Childhood

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ABSTRACT

Inflammatory Bowel Disease (IBD) is common in most industrialised countries and childhood IBD accounts for nearly 30% of total cases. Various studies, mostly from Europe and USA have reported epidemiological characteristics of childhood IBD. The incidence figures vary greatly from region to region and within a region over time. Almost all reported studies have documented an increase in the incidence, mainly of Crohn's disease over the last few decades. The reasons for the increase are not clear but epidemiological observations have led to many postulates. Incidence in developing countries is perceived to be low, but limited data suggest that it may not be as uncommon as previously thought. IBD can occur at any age but is rare in infancy. Among childhood IBD, early onset IBD appears to be different epidemiologically and is characterised by predominance of colonic involvement and high positive family history. It has become apparent that only about 25% of childhood Crohn's disease presents with classical triad of abdominal pain, diarrhoea and weight loss. Pediatricians should be aware of atypical manifestations and should maintain high index of suspicion.

Though epidemiological studies of childhood IBD done so far have contributed towards understanding of IBD, they have differed in study design, population, time period, age group and case definitions. Unfortunately there are no uniform, clear diagnostic criteria which are evidence based. To address this problem, recently the IBD working group of European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has published "The Porto Criteria" which details a consensus based diagnostic criteria for the diagnosis of childhood IBD. This should bring uniformity in ascertainment of newly diagnosed IBD cases. An European multicentre prospective database has also been established to facilitate future epidemiological studies. **[Indian J Pediatr 2006; 73 (8) : 717-721]** *E-mail: Bhupinder-.Sandhu@ubht.swest.nhs.uk*

Key words : *Inflammatory bowel disease; Epidemiology and Childhood*

BACKGROUND

Inflammatory bowel disease (IBD) denotes a group of disorders characterised by chronic intestinal inflammation, the aetiology of which is unknown. It includes Crohn's disease (CD), Ulcerative Colitis (UC) and indeterminate colitis (IC). UC is primarily a mucosal disease with almost exclusive colonic involvement in contrast to CD which may result in mucosal to transmural inflammation of virtually any part of gastrointestinal tract. In a recent very large prospective national study in the British Isles, CD accounted for 60% and UC for 29% of childhood IBD. The remaining 11% constituted IC, where a clear distinction between CD and UC is not possible[1] Data from pediatric IBD consortium registry from the USA has shown similar pattern.[2]

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Epidemiology denotes the study of distribution and determinants of diseases in human population and application of this knowledge to control health problems. IBD is relatively common in most industrialised countries. Epidemiological studies in IBD are important since various epidemiological characteristics like differences in geographic distribution, changes in incidence over time in particular geographic areas, occurrence of IBD within families *etc.* may provide valuable insights into possible etiological factors. Epidemiology of childhood IBD is particularly important as up to 30% of all patients with IBD are diagnosed during childhood. In contrast to adults, IBD in children and adolescents presents closer to disease onset and earlier in the process of intestinal inflammation, potentially enabling better understanding of aetiology. Pediatric IBD patients in general have fewer co-morbid conditions and hence depict natural history of IBD much more accurately. Moreover, parents are more readily accessible for genetic studies which help to improve our understanding of IBD.[3]

In the following sections, we review various epidemiological aspects of childhood IBD:

INCIDENCE

Incidence of IBD in adults may vary significantly from region to region. It is relatively common in industrialised countries of the world, the highest rates being reported in the Scandinavian countries and Scotland followed by England and Southern Europe.[4] The first national prospective survey of childhood IBD was from the British Isles and is the largest prospective study to be reported so far.[5] In this survey, cases of paediatric IBD were identified prospectively for a period of 13 months, from June 1998 to June 1999, *via* British Pediatric Surveillance Unit (BPSU) and British Society of Gastroenterology Research Unit (BSGRU). 1852 pediatricians, pediatric gastroenterologists, surgeons and pathologists in the United Kingdom and Republic of Ireland were sent surveillance cards each month, to be returned whether or not they had a case to report. To identify any children that were cared for by the adult services, BSGRU also sent surveillance cards prospectively to 1395 adult gastroenterologists and Surgeons in the UK. This survey, documented an incidence of 5.2 / 100,000 children aged less than 16 yrs per yr. Several other recent studies have reported incidences of childhood IBD from various other parts of Europe and USA including Sweden,[6,7] Netherlands,[8] Iceland,[9] France[10] and Wisconsin, USA[11] (Table 1). Direct comparison of results of these studies is difficult due to difference in study design, population size, age groups and time periods.

The incidence of IBD in developing countries has been postulated as being low but data is limited. Though infective colitis is much more common, IBD should be suspected and investigated in chronic cases of colitis which have not responded to treatment of common infective agents. It is however, well documented and needs to be remembered that infection for example with Salmonella, may precede or co-exist with IBD.[12]

In 1999, Mehta *et al* from India reported that in their experience, 5% of children admitted for colonic disorders were diagnosed as UC[13] A recent very large, well conducted prospective, adult study from Punjab by Sood et al found that the incidence of UC among this population may be similar to that in the UK.[14] Further studies using modern methodology are needed.

AGE & SEX DISTRIBUTION

IBD can manifest at any age but is rare in infancy. Only 1% of all childhood IBD patients are diagnosed before 1 year of age.[2] The incidence increases steadily during childhood and adolescence, peaking at about 14 years of age. (Fig 1). There is a later peak in adulthood in sixth decade.

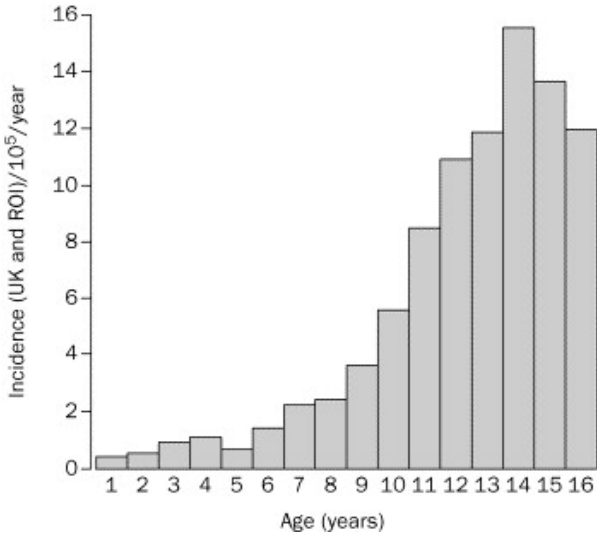

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Fig. 1. Incidence of childhood inflammatory bowel disease in the UK and ROI during 1998 and 1999. All figures are incidence per 100,000 children (95% CI) aged younger than 16 years.

Unlike in adults, pediatric onset CD has clear male preponderance. In the UK study, 62% of pediatric CD in a cohort of 379 children were males.[1] Further examination of sex ratio by the site of disease activity in CD showed that this male excess is seen in nine out of 10 anatomical sites. Only subgroup not to have a male preponderance was those cases without ileal involvement.[1] The reason for this sex bias is not clear. In contrast to CD, pediatric onset UC has equal sex ratio.

Within the group of pediatric IBD, early onset disease appears to have different characteristics. In the study from the British Isles, UC predominated in the under 5 yr age group with only 38% of under 5s accounting for CD

TABLE 1. Recent Incidence Data in Pediatric IBD

Location	References	Year of study	Incidence (new cases / 10^5 / year)			
			IBD total	CD	UC	IC
British Isles	5	1998-99	5.2	3.1	1.4	0.6
Sweden	6	1993-95		1.3	3.2	
Stockholm, Sweden	7	1999-2001	10.5	8.4	1.8	0.2
Netherlands	8	1999-2001	2.1	1.6	3.6	7.3
Iceland	9	1990-94		8.5		
Northern France	10	1997-99		2.6	0.8	0.1
Wisconsin ,USA	11	2000-2001		4.6	2.4	

compared to 61% in children aged 5-16 years.[1] Study of IBD in American children younger than 5 yrs of age showed that, out of 82 children, 44% had UC, 23% had IC and only 33% had CD.[15] More recently, Heyman *et al* reported the pediatric consortium registry data which showed virtually similar results: in 211 children younger than 5 years of age 40% had UC, 24% IC and only 40% CD.[2] In this study, multivariate analysis showed that UC was approximately 2.5 times and IC was 3.5 times more likely in children with IBD who are younger than 8 yrs of age, compared to CD. They also documented that younger the age of onset, higher the rate of family history of IBD. Children younger than 3 years with UC had more frequent first degree relatives with IBD than patients in older age group (44% *vs* 12-24%). A positive family history of IBD in siblings or parents was associated with a 75% increase in the risk of early onset IBD.[2] Thus, from epidemiological standpoint, early onset IBD seems to be different. This group is characterised by predominance of colonic disease (UC, IC or Crohn's colitis). High positive family history of IBD suggests that genetic susceptibility is playing a greater role in the development of the disease in early onset IBD. It has also been observed in several studies that both CD and UC demonstrate genetic "anticipation" *i.e.* disease developing at younger age in offspring than their affected parents.[3]

GEOGRAPHIC VARIATIONS

There may be geographic variations in the type of IBD. In the UK and USA, the incidence of childhood CD exceeds that of UC, similar to overall population data. However, in Sweden and Netherlands, pediatric UC may be more common than CD although in the case of Sweden, the pattern may be changing with CD now becoming more common.[6-8] Studies also have suggested that there may be a north-south gradient with increased incidence of Crohn's in northern latitude,[16] although a larger study across the Europe had concluded that latitude in itself is not a determinant for the occurrence of IBD.[17] Armitage *et al* recently reported increased incidence of juvenile onset CD (0-15 yrs) in northern compared to southern Scotland.[18] In the UK study, the incidence in Scotland (i.e. north) was higher than in England, Wales and Northern Ireland.[1] There does not appear to be any seasonal variation.[19]

TRENDS IN TIME

Many studies have shown a rising trend in incidence of pediatric IBD during last several decades, similar to the adult data. Barton *et al* documented a three fold rise in CD between 1968 and 1983 in Scottish children.[20] Cosgrove *et al* reported more than two fold increase over 11 years between 1983 and 1993 in Wales.[21] Similar increase in incidence was also reported from various other European countries[6,8,22] and the USA.[11] In almost all these studies, the increase was largely due to increase in CD over time, incidence of UC remaining rather unchanged. However, very recent data suggests that incidence of CD may now have reached a plateau and incidence of UC may be rising.[23]

The reason for the increase in incidence of CD is not clear. Though it could partly be due to increased diagnostic accuracy due to advent of flexible endoscopy, improved technology and increased awareness, this is not the whole story. Several studies have attempted to attribute the increase to various epidemiologic/ demographical characteristics. A number of environmental factors such as hygiene, diet, breast feeding, smoking, oral contraceptive pill and infectious agents such as measles, mumps, epstein-barr virus and mycobacterium paratuberculosis have been explored.[24] Smoking appears to predispose to CD but protective against UC.[24] There is no convincing evidence that age at development of IBD is decreasing.[3] Armitage *et al* observed an association of CD with affluence.[18] It has been suggested that this may be due to low level / delayed exposure to common childhood infectious agents due to improved domestic hygiene, resulting in altered immune response in genetically susceptible hosts – the so called "hygiene hypothesis".[25] Extensive research has been undertaken in genetics of IBD. Mutations in NOD2 / CARD 15 gene significantly increase the risk of Crohn's disease and this is particularly associated with ileal location and earlier disease onset.[26] These findings underscore the importance of host-bacterial interactions in the pathogenesis of the IBD, since these genes are involved in mediation of host resistance to bacterial pathogens.

IBD IN ASIANS

Incidence of UC in Asian population resident in western countries appears to be higher than that in native population both in children and adults. Epidemiological studies from Leicestershire in the UK, where a high proportion of residents are immigrants from southern Asia, mostly from India & Pakistan, has shown that mean annual incidence of UC in people of southern Asian origin was significantly higher at 13.7 / 10^5 compared to 6.1 / 10^5 in native Europeans. Among the south Asians, incidence of UC was high in Hindus and Sikhs where as Muslims showed an incidence similar to that of Europeans.[27] In contrast to UC, incidence of CD in Hindus was significantly lower than in Europeans. The mean annual incidences for CD during 1980s were 4.7 / 10^5 in Europeans, 2.4 / 10^5 in Hindus, 3.4 / 10^5 in Sikhs and 5.4 / 10^5 in Muslims.[28] In pediatric IBD, the recent data from British Isles have shown that significantly greater proportion of children of Asian origin feature among under 5s with UC (25% *vs* 6%) with a relative risk of 3.9.[1] The study by Sood *et al* from Punjab, North India, which

involved a study population of 51,910 who were visited at home and had sigmoidoscopy / colonoscopy if symptoms suggested IBD gave a prevalence rate of 44.3 per 100,000. A second visit to the same areas after one year to identify new cases gave an incidence of 6.02 cases per 100,000 per year. These findings are similar to those found by Probert *et al* in Asians resident in Leicester in the UK.[27,28] Epidemiological data from developing countries on childhood IBD is scanty.

PRESENTING FEATURES

Abdominal pain, diarrhoea and weight loss were considered to be the "classic triad "of CD. However, it has been well documented and become apparent that now only a minority of CD children present with this classical triad.[1] It is interesting to note the change in the clinical presentation of childhood CD over the last two decades. Data from the hospital for sick children in Toronto during the period of 1980-1989, showed that nearly 80% of CD children presented with the triad of abdominal pain, diarrhoea and weight loss.[3] However, more recent population based survey of childhood IBD carried out in the British Isles during 1998-99, found that only 25% presented with this classic triad. 44% of CD did not report diarrhoea.[1] Table 2 shows the presenting features of childhood IBD form this survey. In contrast to CD, majority of UC and IC children presented with diarrhoea and bleeding.

Health professionals need to be aware of these in order to diminish the delay in the diagnosis. It has been shown that there is a negative correlation between length of delay and height in CD. Wider use of screening blood tests to look for raised erythrocyte sedimentation rate, C-reactive protein, platelets and reduced albumin may help earlier identification of CD cases[1] and presence of perinuclear antineutrophil cytoplasm antibody (pANCA) in UC may help to differentiate between UC and infective colitis.

TABLE 2. Presenting Symptoms and Signs of Childhood IBD

	CD (n=379)	IC (n=72)	UC (n=172)
Common symptoms			
Abdominal pain	274 (72%)	54 (75%)	106 (62%)
Diarrhoea	214 (56%)	56 (78%)	127 (74%)
Bleeding	84 (22%)	49 (68%)	145 (84%)
Weight loss	220 (58%)	25 (35%)	53 (31%)
Lethargy	103 (27%)	10 (14%)	20 (12%)
Anorexia	94 (25%)	9 (13%)	11 (6%)
Other symptoms			
Arthropathy	28	3	11
Nausea / vomiting	22	1	1
Constipation / soiling	4		
Psychiatric symptoms	3		
Secondary amenorrhoea	1		1
Signs			
Anal fistula	17		
Growth failure / delayed puberty	14	1	
Anal abscess, ulcer	8		
Erythema nodosum / rash	6		1
Liver disease	3	2	5
Appendicectomy	2		
Toxic megacolon			1

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DISEASE DISTRIBUTION

Though traditionally CD was considered to be mainly a disease involving terminal ileum, routine use of various investigative techniques including upper and lower gastrointestinal endoscopy, barium meal follow-through, barium enema and radiolabelled white cell scans have shown disease distribution to be more widespread.

Although childhood CD most commonly affects terminal ileum and right colon, in the UK study, 50% also had gastro-duodenal involvement and 20% had jejunal involvement. Only 9% had isolated small bowel involvement and 7% isolated colonic disease.[1] Recent American study documented that gastro-duodenal involvement was present in 5% of 0-5 yr olds, 10% of 6-12 yr olds and 13% of 13-17 yr olds, suggesting that proportion of patients with gastro-duodenal involvement slightly increased with age.[2] Colonic involvement predominates when CD is diagnosed in younger children.[1, 2-15] Heyman *et al* reported isolated colonic CD in 32% of children younger than 6 yrs of age, 20% of 6-12 yr olds and 24% of 13-17 yr olds.[2]

Childhood UC, unlike adult onset UC, is much more extensive at presentation. 81% of children with UC have disease extending to right colon, majority having a pancolitis with only 4% having disease limited to the rectum.[1] This underscores the importance of a full colonoscopy in establishing the extent of the disease in children.[29]

CONCLUSION

Epidemiological studies in childhood IBD have contributed significantly to our understanding of IBD. So far, studies have largely focussed on the incidence, clinical features and how these features differ based on geographic location, demographic influence, ethnicity and over time. Reported incidence figures vary greatly. Comparing disease rates between and with in areas at different time intervals, and identifying areas of increased / rapidly changing incidence will give invaluable clues and allow more focussed investigation towards possible environmental , genetic or other risk factors. Comparison between the results of studies reported so far is difficult because of different criteria and designs. Multicentre and multinational collaboration is essential to undertake such studies. IBD working group of

first world congress of Pediatric Gastroenterology Hepatology and Nutrition identified various epidemiologic issues to be addressed including developing population based, prospective and standardised databases to determine and track incidence, prevalence, disease behaviour, potential risk factors, effect of therapy and others.[24] This is possible only if commonly agreed on disease definitions and diagnostic criteria are used, since there is absence of clear, evidence based criteria. Aiming towards this, Inflammatory bowel disease working group of European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has recently defined, in its medical position paper, a consensus based criteria for diagnosis of childhood IBD and has made recommendations which was named as "The Porto Criteria" as the meeting was held in Porto, Portugal.[29] Several European centres will endeavour to follow these recommendations which will allow a compact database of uniformly defined, prospectively collected pediatric IBD cases. This will serve as a nucleus for research into various aspects of childhood IBD including genetics, drug therapy, health outcomes socioeconomic impact *etc.* and greatly facilitate future research on aetiology and pathophysiology of childhood IBD. It is hoped that this criterion will be used universally. Unfortunately, there are very limited data on childhood IBD from the developing countries. Prospective studies in children are very much needed from India and other countries.

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Notes and News

PPSA: Pediatric Procedural Sedation and Analgesia Course

3rd December, Sunday, 2006

The Department of Pediatrics at Centre for Child Health, Sir Ganga Ram Hospital, Delhi and IAP Intensive Care Chapter - Emergency Cell are organizing **"PPSA: Pediatric Procedural Sedation and Analgesia Course".** The course will be conducted at Sir Ganga Ram Hospital, New Delhi by eminent faculty in the field of Pediatric Emergency Medicine. The registration is restricted to 30 delegates on first come first serve basis. Those who have done the PALS Course will be given priority. There is no spot registration. The registration fee is Rs. 1000/- (including course material) which may be sent by cheque/cash/bank draft in favor of "Ambulatory Pediatrics" to the Course Director, Dr. Suresh Gupta, Consultant, Pediatric Emergency Medicine, Department of Pediatrics, Sir Ganga Ram Hospital, New Delhi-110060, Phone : 9811426628, 28312656, 28312591, E-mail : drguptasuresh@yahoo.co.in

PALS Provider Course

20-21 January 2007

The Department of Pediatrics at Centre for Child Health, Sir Ganga Ram Hospital, Delhi and Indian Academy of Pediatrics, Delhi are organizing "PALS Provider's Course" on 20-21 January 2007. The course will be conducted at Sir Ganga Ram Hospital, New Delhi by eminent senior faculty. The registration is restricted to 40 delegates on first come first serve basis. There is no spot registration. The registration fee is Rs 2000/- (including course material) that may be sent by cheque/cash/bank draft in favor of "Sir Ganga Ram Hospital". Contact Course Coordinator, Dr. Suresh Gupta, Consultant, Pediatric Emergency Medicine, Department of Pediatrics, Centre for Child Health Sir Ganga Ram Hospital, New Delhi-110060, Phone : 9811426628, 28312656, 28312591, E-mail : drguptasuresh@yahoo.co.in

APLS: The Pediatric Emergency Medicine Course

24-25 March 2007

The Department of Pediatrics at Centre for Child Health, Sir Ganga Ram Hospital, Delhi and IAP-Intensive, Care Chapter-Emergency Cell are organizing "APLS: The Pediatric Emergency Medicine Course" on 24–25 March 2007. The course will be conducted at Sir Ganga Ram Hospital, New Delhi by eminent faculty in the field of pediatric emergency medicine. The registration is restricted to 40 delegates on first come first serve basis. There is no spot registration. The registration fee is Rs 1800/- (including course material) which may be sent by cheque/cash/bank draft in favor of "Ambulatory Pediatrics" to the Course Director, Dr. Suresh Gupta, Consultant, Pediatric Emergency Medicine, Department of Pediatrics, Sir Ganga Ram Hospital, New Delhi-110060, Phone : 9811426628, 28312656, 28312591, E-mail : drguptasuresh@yahoo.co.in

State-of-the-art Workshop on Neonatal Resuscitation

A State-of-the-art workshop on Neonatal Resuscitation (*as per latest 2006 guidelines*) is being organized by the Department of Pediatrics, AIIMS, on Sunday 6th August 2006 (9.00 am to 5.00 pm). The workshop is targeted for practicing pediatricians/obstetricians and postgraduate students. Registration would be limited to 20 participants on the first-come-first-served basis. The total participants will be 40; remaining 20 are reserved for left-outs of 2nd April workshop. Please send a draft of Rs. 750/- drawn in favour of "*CME Programme in Neonatalogy",* payable at New Delhi latest by 30th June, 2006. Participants will be provided with latest resource book at least two weeks before the workshop. Please note there will be no provision for spot registration. For further details, please contact Dr. Ramesh Agarwal, Assistant Professor, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi–110029. Tel. 001–26593621 Fax No. : 011-26862663, e-mail : aranag@rediffmail.com