World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i48.10653

World J Gastroenterol 2016 December 28; 22(48): 10653-10662
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Variable outcome in infantile-onset inflammatory bowel disease in an Asian cohort

Way Seah Lee, Ruey Terng Ng, Koon-Wing Chan, Yu-Lung Lau

Way Seah Lee, Ruey Terng Ng, Department of Paediatrics, University Malaya Medical Center, Kuala Lumpur 59100, Malaysia

Way Seah Lee, University Malaya Paediatric and Child Health Research Group, University Malaya, Kuala Lumpur 59100, Malaysia

Koon-Wing Chan, Yu-Lung Lau, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China

Author contributions: Lee WS conceived the concept and wrote the first draft; both Lee WS and Ng RT collected the clinical data and performed data analysis; Chan KW and Lau YL performed the mutational analysis; Lau YL provided critical analysis of the manuscript.

Supported by a research grant from Ministry of Higher Education, Malaysia (UM.C/625/HIR/MOHE/CHAN/13/1); Hong Kong Society for the Relief of Disabled Children (to Chan KW and Lau YL).

Institutional review board statement: The present study was reviewed and approved by the Medical Ethics Committee of University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Informed consent statement: The legal guardians of all patients described in the present study gave informed written consent for mutational analysis performed for the present study.

Conflict-of-interest statement: The authors have declared that no competing interests exist.

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Way Seah Lee, Professor, Department of Paediatrics, University Malaya Medical Center, Lembah Pantai, Kuala Lumpur 59100, Malaysia. leews@um.edu.my
Telephone: +66-603-79492065
Fax: +66-603-79494704

Received: March 5, 2016
Peer-review started: March 8, 2016
First decision: April 14, 2016
Revised: August 31, 2016
Accepted: October 19, 2016
Article in press: October 19, 2016
Published online: December 28, 2016

Abstract

AIM

Infantile-onset inflammatory bowel disease (IO-IBD) with the onset of disease before 12 mo of age, is a different disease entity from childhood IBD. We aimed to describe the clinical features, outcome and role of mutation in interleukin-10 (IL-10) and interleukin-10 receptors (IL-10R) in Asian children with IO-IBD.

METHODS

All cases of IO-IBD, defined as onset of disease before 12 mo of age, seen at University Malaya Medical Center, Malaysia were reviewed. We performed mutational analysis for *IL10* and *IL10R* genes in patients with presenting clinical features of Crohn's disease (CD).

RESULTS

Six [13%; CD = 3, ulcerative colitis (UC) = 2, IBD-unclassified (IBD-U) = 1] of the 48 children (CD = 25; UC = 23) with IBD have IO-IBD. At final review [median (range) duration of follow-up: 6.5 (3.0-20) years], three patients were in remission without immunosuppression [one each for post-colostomy (IBD-U), after standard immunosuppression (CD), and after total colectomy (UC)]. Three patients were on immunosuppression:

one (UC) was in remission while two (both CD) had persistent disease. As compared with later-onset disease, IO-IBD were more likely to present with bloody diarrhea (100% *vs* 55%, *P* = 0.039) but were similar in terms of an associated autoimmune liver disease (0% *vs* 19%, *P* = 0.31), requiring biologics therapy (50% *vs* 36%, *P* = 0.40), surgery (50% *vs* 29%, *P* = 0.27), or achieving remission (50% *vs* 64%, *P* = 0.40). No mutations in either IL10 or IL10R in the three patients with CD and the only patient with IBD-U were identified.

CONCLUSION

The clinical features of IO-IBD in this Asian cohort of children who were negative for *IL-10* or *IL-10R* mutations were variable. As compared to childhood IBD with onset of disease after 12 mo of age, IO-IBD achieved remission at a similar rate.

Key words: Infantile-onset inflammatory bowel disease; Pediatric

Core tip: We described the clinical features, outcome and role of mutation in *IL-10* and *IL-10R* in Asian children with infantile-onset inflammatory bowel disease (IO-IBD). We reviewed all cases of IO-IBD, defined as onset of disease before 12 mo of age, seen at a single center in Malaysia. We conclude that the clinical features of IO-IBD in this Asian cohort of children were variable. IO-IBD achieved remission at a similar rate, were more likely to discontinue immunosuppression therapy at final review and not more likely to require biologics therapy or surgery.

Lee WS, Ng RT, Chan KW, Lau YL. Variable outcome in infantile-onset inflammatory bowel disease in an Asian cohort. *World J Gastroenterol* 2016; 22(48): 10653-10662 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i48/10653.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i48.10653

INTRODUCTION

Most of the patients with inflammatory bowel disease (IBD) have the onset of disease during adolescence or early adulthood[1,2]. There is a well-documented increase in the incidence of IBD with an onset of disease within the first two decades of life[3]. In childhood IBD, the disease phenotype and subsequent disease course are influenced by the age at first diagnosis[4]. In a large North American cohort of childhood IBD, those who had an onset of disease between 1 to 5 years (very early-onset) were more likely to have a mild disease at diagnosis but a more aggressive phenotype over time as compared to children who had an onset between 6 to 10 years of age[4].

The development of IBD in infancy is extremely rare[1]. Data from epidemiological studies and IBD registries, mostly from North America and Europe, suggest that less than 1% of children with IBD have an onset during the first 12 mo of life[5-9]. Crohn's disease (CD) appeared to be more common than ulcerative colitis (UC) in these studies[5-8]. However, a recent large cohort study from North America involving close to 2000 cases of childhood IBD did not identify any cases with an onset of disease < 1 year of age[4].

The current concept of the pathogenesis of IBD is that it develops in genetically susceptible hosts with an altered intestinal response to various external stimuli[10,11]. In infantile-onset (IO-) IBD, monogenic diseases causing persistent intestinal inflammation, such as Wiskott-Aldrich syndrome and hyper-IgM syndrome, are well documented[12,13]. Mutations in genes encoding the interleukin-10 (*IL10*) or interleukin-10 receptors (IL10R) subunit proteins have been discovered in patients with IO enterocolitis, usually within the first three months of life[14-18]. These infants have severe perianal disease and extra-intestinal features such as folliculitis and arthritis[14-17]. In some cases, hematopoietic stem cell transplant (HSCT) is curative in IBD secondary to IL10/IL10R deficiency[14-17]. Nevertheless, it has been shown that the majority of patients with severe infantile colitis produce and respond to IL10 normally[15], suggesting additional pathways to inflammation and the complex nature of the pathogenesis of infantile-onset inflammatory bowel disease (IO-IBD)[19].

IBD is not as common in Asians as in the Caucasians[20]. We reported the first case of IO-IBD in an Asian infant due to mutations in the IL10R by using exome sequencing[21]. Subsequently, other authors have also reported early-onset IBD due to mutations in IL-10R[22]. The aims of the present study were to describe the phenotypic characteristics and outcome of IO-colitis in a cohort of Asian children and to define the role of *IL10* and *IL10R* mutations in these patients.

MATERIALS AND METHODS

The present study was a retrospective review of all patients with childhood IBD who were seen at the Department of Paediatrics, University Malaya Medical Center (UMMC), Kuala Lumpur, Malaysia, from 1996 to 2014. During the study period, UMMC was the major referral center for pediatric IBD for entire Malaysia, serving both peninsular Malaysia and East Malaysia. The present study was funded by the High Impact Research Fund from Ministry of Higher Education, Malaysia (UM.C/625/HIR/MOHE/CHAN/13/1) and was approved by the institutional ethical committee of UMMC (UMMC 975.7). Written informed consent was given by the parents of the children for their clinical record, as well as the results of the mutational analysis to be used in the present study.

Patients

The medical records of all children younger than 18 years of age who have a diagnosis of IBD were reviewed. Patients who have the onset of the disease in the first 12 mo of age were included. Data on all children aged ⩽ 18 years of age with a diagnosis of IBD who are currently followed up at the department were also reviewed. The following patients were excluded: (1) patients with incomplete medical data; or follow-up or outcome data were incomplete; and (2) patients with an alternative diagnosis, such as infective, allergic, or iatrogenic (*i.e.,* radiation colitis or graft-*vs*-host diseases) causes of colitis.

Diagnosis

The patients were diagnosed to have CD, UC or IBD-unclassified (IBD-U) according to established clinical, biochemical, radiologic, endoscopic, and histologic criteria[23,24]. In UMMC, all patients suspected of having an IBD were investigated according to the recommendations by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition[23]. In addition, congenital or acquired immune deficiencies causing infantile colitis such as human immunodeficiency virus infection (HIV), severe combined immune deficiency (SCID), chronic granulomatous disease, hyper-IgM syndrome, and Wiskott-Aldrich syndrome were excluded by complete blood count, platelet count, peripheral blood film, HIV serology, immunoglobulins level (IgG, IgA, IgM and IgE), lymphocyte subset, nitroblue tetrazolium test, and anti-enterocyte antibody.

The diagnosis of IBD required endoscopic evaluation, including histologic assessment of mucosal pinch biopsies. All patients underwent esophagogastroduodenoscopy (EGDS) and colonoscopy. Multiple mucosal biopsies were reviewed by clinical pathologists. Stool studies were performed in all patients to exclude infectious causes of diarrheal illness. Disease location and behavior were classified according to the Paris Classification of Pediatric IBD[24]. Features which favor the diagnosis of CD are extensive endoscopic inflammation of the upper gastrointestinal tract; presence of perianal disease; normal looking rectum; presence of stenosis, cobblestoning, and linear ulceration in the ileum; and macroscopic ileitis in the presence of normally looking cecum[24]. Histological features favoring CD include microscopically normal appearing skip lesions as well as presence of well-formed granuloma remote from ruptured crypts[24].

Medical therapy

In children with CD, exclusive enteral nutrition (EEN) was the initial treatment of choice. In children who were unable to comply with EEN, or who did not respond to EEN, corticosteroid (CS; 1-2 mg/kg body weight, maximum 60 mg) was the initial immunosuppression of choice[25]. Azathioprine (Aza) at a maximum dose of 2.5 mg/kg body weight was used as steroid-sparing drug[25,26]. Monitoring of the therapeutic levels for Aza or determination of thiopurines methyltransferase genotype or phenotype were unavailable in the unit throughout the study period. The clinical response to Aza was closely observed while its side effects such as acute pancreatitis and marrow suppression were regularly monitored[26]. Infliximab (IFX) was used in children with refractory disease, fistulating CD, or in luminal CD despite optimal immunomodulatory therapy[25,26]. The IFX was administered in dose of 5 mg/kg body weight at weeks zero, two and six, followed by 8-weekly infusions[25]. This dosing regimen was adjusted according to the response of the patients, either by shortening the duration between two consecutive infusions, or an increase in the dose administered (maximum 10 mg/kg). No therapeutic level of IFX or antibodies against IFX was available within the country or the region during the study period. Adalimumab (Ada) was given to patients who developed a loss of effect to IFX. Ada was administered subcutaneously at week zero and two (160 mg and 80 mg, or 80 mg and 40 mg, for body weight ⩾ 40 kg or < 40 kg) and subsequently 40 mg every other week irrespective of body weight[27].

Data collection

The following data were collected: demographic data, clinical features, radiologic and histologic findings, medical and surgical therapies if applicable, and disease status at final review. Patients with CD were considered to have inactive disease if the Pediatric Crohn Disease Activity Index score was ⩽ 10, while patients with UC were considered to be in remission if the Pediatric Ulcerative Colitis Index was ⩽ 10[28,29].

Comparisons were made between patients with IO-IBD and patients who have an onset of disease after the first year of life (defined as later-onset disease) in their presenting features, immunosuppressive therapy and the need for surgery, as well as disease status at final review.

Mutational analysis

Blood samples were obtained from patients and their parents for mutational analysis after obtaining written informed consent. The analysis was performed at the Research Laboratory of the Department of Paediatrics and Adolescent Medicine, the University of Hong Kong. The genomic PCR was performed using the HotStarTaq® Plus PCR system (Qiagen GmbH, Germany). Between 10-100 ng of genomic DNA was amplified using the sense and antisense primers, flanking the coding regions and splice junctions, according to the manufacturer's protocol. DNA sequencing was performed on both strands using BigDye Terminator v3.1 Cycle Sequencing Kit and 3730xl DNA Analyzer (Applied Biosystems CA., United States). Homology analysis with the reference genomic sequence was

performed using the NCBI program BLAST (http://blast.ncbi.nlm.nih.gov/Blast.cgi). The mutations screened for the purpose of the present study are shown in Supplementary material.

Statistical analysis

Data were managed with IBM SPSS statistical package version 21.0.0 for Windows. Dichotomous measures were compared by means Fisher exact test. Statistical significance was set at a P value of < 0.05.

RESULTS

During the study period, a total of 48 children with a diagnosis of IBD (CD = 25, UC = 23) were followed up at the Department of Paediatrics of UMMC. Of these, six (13%) had the onset of disease within the first year of life (IO-IBD). According to the Paris Classification for Pediatric IBD[24], two of the six patients had UC, three had CD, and one had IBD-U.

Demography

There were four males and two females. None of the patients has any first degree family members who also have IBD or other autoimmune conditions. With the exception of patient No. 1, none of the patient had any significant perinatal history. The age of onset of first symptom ranged from first week to 12 mo of life (median 5 mo; Table 1).

Phenotypic characteristics

Phenotypically, the patients can be classified into CD (n = 3), UC (n = 2), and IBD-U (n = 1) at initial presentation, but the subsequent disease course was diverse.

Clinical presentation

All the children presented initially with bloody diarrhea (Table 1). One patient was diagnosed to have postnatal cytomegalovirus (CMV) infection at birth. Oral ulcers were noted in one patient with CD while perianal disease was present in two of the three patients with CD and the infant with IBD-U.

Associated medical and autoimmune conditions

None of the patients developed other autoimmune diseases. One patient (infant No. 3) developed developmental regression at seven years of age with course tremors. No etiology can be ascertained despite extensive investigations. Investigations for immune system did not reveal the presence of immunodeficiency.

UC

Patient No. 1 developed watery, non-bloody diarrhea on third day of life (Table 1), and was started on extensively hydrolyzed and amino acid-based formulae. The diarrhea became bloody from three months onwards. When referred at our center at four months of age, there was no oral ulcer or perianal disease. During bowel rest and total parenteral nutrition, there was no diarrhea, but diarrhea promptly resumed when extensively hydrolyzed formula was introduced. A colonoscopy showed pancolitis with inflamed mucosa and friability but no ulceration. The rectum, sigmoid and descending colon were the most severely affected. Histologically, there was dense lymphoplasmacytic and eosinophilic infiltration of the colonic mucosa. A course of oral CS failed to improve his symptoms. The diarrhea gradually improved with amino acid-based formula. The stool frequency improved but was persistently blood stained.

There was a relapse of bloody diarrhea at sixteen month of age when the child was gradually weaned off from amino acid formula to a normal diet. Repeated courses of CS and a course of oral cyclosporin failed to improve his symptoms. A total colectomy was performed. Macroscopically, the entire colon was pale in appearance with prominent submucosal vascular pattern, indicating mucosal atrophy. No ulcers were noted. Histologically the mucosa was thin. There were areas of patchy inflammation, with evidence of chronic inflammation, dense lymphoplasmacytic infiltration in the mucosa, sparing the submucosa, muscular layer and serosa. There was no crypt branching, or irregularity in the shape and sizes of the crypt. There was also scant eosinophilic infiltration. The child remained symptom free after total colectomy.

CD

Patient No. 3 developed symptoms of recurrent bloody diarrhea at the age of seven months (Table 1). A diagnosis of postnatal CMV infection was made at another hospital at the age of three months due to persistent neonatal cholestasis. The IgM for CMV was positive. The jaundice subsided at the age of six months. The bloody diarrhea was intermittent in nature. At referral to our unit at two years of age, the child had failure to thrive, abdominal pain and bloody diarrhea, with multiple perianal fistulae and abscesses. EGDS showed duodenitis. Colonoscopy showed extensive ulceration with pseudopolyps formation. EEN was commenced, together with antibiotics, CS and Aza. IFX was given in view of severe perianal disease. After one year, there was improvement in general condition but minimal improvement in the perianal disease. He was noted to have three episodes of pneumonia and two episodes of herpes zoster infection when he was receiving IFX therapy. However, no recurrent infections were noted when the therapy was discontinued. In addition, investigations into an underlying immunodeficiency were negative.

A defunctioning colostomy was performed at six years of age. There was persistent perianal disease. A course of Ada (six doses) was given with no improvement. A repeat colonoscopy showed extensive

Table 1 Phenotypic characteristics, disease behavior, therapy and outcome in six Asian children with infantile-onset inflammatory bowel disease

Patients' initials	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
Sex	Male	Male	Male	Male	Female	Female
Ethnicity	Chinese	Chinese	Malay	Chinese	Indian	Malay
Consanguinity	No	No	No	No	No	No
Breast feeding (duration)	No	No	No	Yes (3 mo)	Yes (2 mo)	Yes (4 mo)
Age at onset	First week	12 mo	7 mo	2 mo	6 mo	4 mo
Disease phenotype	EC→UC	UC	CD	CD	CD	IBD-U
Major symptoms at presentation	Bloody diarrhea and PR bleeding	Bloody diarrhea, anemia	Oral ulcers, bloody diarrhea, abdominal pain	Bloody diarrhea, abdominal pain	Bloody diarrhea, growth faltering	Bloody diarrhea
Perianal disease	Nil	Nil	Abscess and fistula	Abscess and fistula	Nil	Abscess and fistula
Other medical or autoimmune conditions	Nil	Nil	Nil	Nil	Nil	Nil
Recurrent infections	Nil	Nil	Congenital CMV infection,	Nil	Nil	Nil
Disease location[1]	E4S1	E4	L3L4a	L3L4a	L3	L2
Disease behavior/ severity[1]	S1	S1	B2B3p	B2B3p	B1	B1p
Histopathology	Dense lymphoplasmacytic and eosinophilic infiltration of the lamina propria involving the gastric mucosa, duodenum and colonic mucosa.	Colonic mucosa showed mild degenerative atypia, cryptitis and crypt abscesses. Lamina propria showed increase in neutrophilic and lymphoplasmacytic infiltration.	Lymphocytic infiltration of lamina propria. No granuloma or crypt abscess seen. The duodenum showed chronic inflammation.	Lymphocytic infiltration of lamina propria. No granuloma or crypt abscess seen	Mild inflammation in the lamina propria with lymphocytes and plasma cells. No granuloma or crypt abscess	First biopsy: transmural inflammation involving all layers of bowel wall, including the skeletal muscle with dense lymphoplasmacytic infiltration. No crypt abscess seen. Second biopsy: colonic mucosa inflammed but the architecture was preserved. Significant lymphoplasmacytic and neutrophilic infiltration mainly confined to the lamina propria
Other associated diseases	Nil	Nil	Developmental regression at 6 yr age	Nil	Nil	Nil
Mutational analysis	Not done	Not done	Not detected	Not detected	Not detected	Not detected
Medical therapy	CS, CsA, enteral nutrition	CS, Aza	CS, Aza, IFX × 24 doses	EN, CS, Aza, IFX × 14 doses	Aza, IFX × 3 doses	Nil
Surgery	Total colectomy at 18 mo	Nil	Ileostomy at 6 yr of age	Nil	Nil	Ileostomy; closure at 18 mo of age
Age at last follow up	21 yr	6 yr	9 yr	6 yr	13 yr	3 yr
Final clinical status	Alive, deafness due to aminoglycosides. in remission, off therapy for 18 yr	Alive, in remission; on Aza	Alive, persistent disease, on CS, Aza. Developmentally delayed.	Alive, persistent disease, on CS, Aza and IFX. Parents refused surgery	Alive, in remission; off therapy for 2 yr	Alive, in remission; no therapy

[1]According to Levine *et al*[24]. Aza: Azathioprine; CD: Crohn's disease; CMV: Cytomegalovirus; CS: Corticosteroid; CsA: Cyclosporin; EC: Eosinophilic colitis; EN: Enteral nutrition; IFX: Infliximab; PR: Per rectal; UC: Ulcerative colitis.

colonic ulceration. There was persistent and severe perianal disease. EEN (amino acid-based formula) was recommenced in addition to low dose CS (10 mg). Repeated courses of oral antibiotics (amoxicillin, doxycycline, metronidazole and vancomycin) were also given[30]. The condition improved with this regime with a reduction of the number of bloody stools. The perianal disease became quiescent with no abscess or fistula.

IBD-U

Infant #6 developed chronic bloody diarrhea at four months of age. She has been breast-fed exclusively since birth. She was given repeated courses of antibiotics even though the stool studies were negative for any pathogens. Subsequently she had several

Table 2 Comparison of disease characteristics, management and final outcome of infantile-onset inflammatory bowel disease and children with onset of disease after 12 mo of age

	Onset before 1 year, *n* (%)	Onset after 1 year, *n* (%)	*P* value
n	6	41	
Median age at diagnosis (yr)	0.44	8.34	
Duration of follow-up (yr), median (range)	6.1 (1.4-19.6)	8.3 (1.0-16.6)	
Male	4	22	
Female	2	19	
Crohn's disease	3	22	
Ulcerative colitis	2	19	
IBD-unclassified	1	0	
Initial presentation, *n* (%)			
Bloody diarrhea	6 (100)	23 (55)	0.039
Perianal disease	3 (50)	8 (19)	0.11
Extraintestinal involvement			
Autoimmune liver disease	0 (0)	8 (19)	0.31
Therapy			
Biologics-infliximab	3 (50)	15 (36)	0.40
Surgery	3 (50)	12 (29)	0.27
Disease status at final review			
Inactive disease or in clinical remission	3 (50)	27 (66)	0.40
Discontinuation of immunosuppression			
Yes	3 (50)	5 (12)	0.053
No	3 (50)	36 (88)	

IBD: Inflammatory bowel disease.

perianal abscesses and fistulas requiring incision and drainage. She was seen at another hospital at five months of age, where a limited sigmoidoscopy showed extensive, deep linear ulceration up to the sigmoid colon. A sigmoidal colostomy was performed. Histological examination of the bowel tissue obtained during the operation showed transmural inflammation involving the muscular layer and the serosa. After the colostomy, the child improved with weight gain and a complete cessation of diarrhea. No immunosuppression treatment was started.

When seen at our hospital at seven months of age, the perianal area was quiescent with a skin tag. No abscess was noted. An EGDS was normal. A colonoscopy showed multiple flat nodules with relatively normal mucosa over the rectum. The remaining colon was pale with loss of normal vascular pattern. There were no pseudopolyps, mucosal ulcerations or friability. Histologically, the colonic mucosa was inflamed. The tubular glands were devoid of significant architectural distortion. The lamina propria showed marked infiltration by lymphoplasmacytic cells with the formation of lymphoid follicles and mild neutrophilic infiltrates. There were occasional cryptitis, but no crypt abscess or granuloma was noted.

She received nutritional supplement. No immunosuppressive therapy was started. A repeat EGDS and colonoscopy at 14 mo of age were entirely normal macroscopically. Histologically the colonic architecture was well preserved with minimal lymphoplasmacytic infiltration. A closure of the colostomy was performed at 15 mo of age. Postoperatively she remained well and asymptomatic. The clinical presentation, colonoscopic appearance and histologic features were classically that of CD, but the subsequent course, *i.e.*, sustained remission without immunosuppression made a diagnosis of CD unlikely. Hence a diagnosis of IBD-U was made.

Medical and surgical therapies

Five of the six patients had immunosuppressive therapies consisted of CS, Aza, cyclosporin and IFX. In addition, one patient (infant No. 1) who had an initial diagnosis of allergic colitis also had elemental diet. All the three patients with CD were given IFX (see above).

Three patients required surgery: one had total colectomy, one had colostomy and another had ileostomy.

Final disease status

At final review (median duration of follow up: 5.5 years; range 2.0-20 years), all patients survived. Of these, three patients (50%) were in complete remission, two patients with CD had inactive disease with no immunosuppression while one patient with UC was in remission after total colectomy (Table 1). One patient with UC was in remission with Aza. Two patients have active disease despite adequate immunosuppressive therapies at a recommended dose.

Comparison with patients with later-onset disease

A comparison was made between the IO-IBD described in the present study and other patients with later-onset IBD (onset of disease after 12 mo of age) who were followed up at the department (Table 2). As compared to patients with later-onset disease, children with IO-IBD were more likely to have bloody diarrhea at presentation (100% *vs* 55%, $P = 0.039$) but were not more likely to have an associated autoimmune liver disease (0% *vs* 19%, $P = 0.31$), require the use of biologics (50% *vs* 36%, $P = 0.40$), or surgery (50% *vs* 29%, $P = 0.27$), or achieving remission at final review (50% *vs* 64%, $P = 0.40$). However, there was a trend for patients with IO-IBD to discontinue immunosuppressive therapy (50% *vs* 88%, $P = 0.053$).

Comparison with Caucasian patients

A comparison was made between patients described in the present study and those reported in the literature (Table 3). Three other studies, all from European centers, described IO-IBD[8,9,14]. Generally patients with IO-IBD required aggressive immunosuppression. Between 19% and 33% of the patients had surgery. However, prolonged remission, some without immunosuppression, was achieved in 67% to 100% of patients.

Mutational analysis

Mutational analysis for coding regions together with

Table 3 Clinical characteristics, management and outcome of infantile-onset inflammatory bowel disease in selected series

	Ref.	Patients in all age group), *n* (%)	Nature of patients, *n* (%)	Age of patients at onset of disease	Duration of follow-up (yr), median (range)	Medical therapies	Surgery, *n* (%)	Disease status: remission of survivors at final review, *n* (%)	Deaths
1	Ruemmele *et al*[8]	10 (2.5)	CD = 4 (40) UC = 2 (20) IC = 4 (40)	First 12 mo	2.5 (2.5-8)	Bowel rest, PN, CS, Aza, CsA	3 (30); 2 colectomy, 1 ileostomy	10 (100); off therapy, 2 (20); ongoing therapy, 8 (80)	None
2	Cannioto *et al*[9]	16 (8.6)	CD = 6 (37.5) UC = 8 (50) Indeterminate = 2 (12.5)	First 2 yr	6 (4-22)	Aggressive multi-drug therapy, Aza, IFX, thalidomide, CsA	3 (19); 2 colectomy, 1 ileostomy	11 (100); off therapy, 4 (25); ongoing therapy, 6 (38), after BMT, 1 (6)	5 (mortality rate 31%)[1]
3	Begue *et al*[15]	13 (-)	All had pancolitis, 6 had small bowel involvement[2]	First 12 mo	-	-	4 (31)	All required immuno-suppressive therapy. Final disease status not described	Not described
4	Present study, Malaysia, 2016	6 (13)	CD = 4 (67) UC = 2 (33)	First 12 mo	5 (1.5-20)	Bowel rest, steroids, Aza, CsA, INF	3 (33); 1 colectomy, 2 ileostomies	4 (67); off therapy, 3 (50); ongoing therapy, 1 (17); not in remission, 2 (33)	None

The authors included IBD and IBD-mimicking enterocolitis; [1]Two deaths were related to infections; one death each for interstitial pneumonia, post-BMT, and giant cell hepatitis progressing to liver failure; [2]The authors did not classify the patients into either Crohn's disease (CD), ulcerative colitis (UC) or indeterminate colitis (IC). Aza: Azathioprine; BMT: Bone marrow transplantation; CS: Corticosteroid; CsA: Cyclosporin; IBD: Inflammatory bowel disease; IFX: Infliximab; PN: Parenteral nutrition.

splice junctions of *IL10* and *IL10R* were performed by genomic Sanger sequencing of the three patients with CD and one infant with IBD-U. No causative mutation was identified.

DISCUSSION

Inherited genetic defect leading to immune dysregulation, the influence of intestinal microbiome and environmental factors have all been considered playing an important role in the pathogenesis of IBD, including IO-IBD[14]. Mutations in IL10 and IL10R have been identified in a subset of infants with severe IO-IBD[13-17,20], often presenting with perianal fistulae, respond poorly to medical therapies and needing early surgical interventions[16]. HSCT has been shown to be curative in IBD secondary to IL10/IL10R deficiency[13-16].

However, clearly not every young child with IO-IBD have mutations in IL10 or IL10R[14,15]. Of the 13 infants with IO-IBD reported by Begue *et al*[15], only two (15%) were found to have a deficient IL10 signaling[14]. Instead the authors found additional compromised signaling in IL22 in a patient with absent IL10RB[14]. Similarly, Shim *et al*[22] reported that only seven (50%) of the 14 Korean infants with IO-IBD had mutations in IL10RA. Thus it is likely that IO-IBD represents a heterogeneous group of disorders with the common feature of early-onset severe colitis within the first weeks to months of life[8,9,14,22]. Mutations in *IL10* and *IL10R* may be responsible in a significant proportion of, but not all, young children with IO-IBD. Uhlig *et al*[13] have shown that many other monogenic disorders and primary immunodeficiencies, including SCID and Wiskott-Aldrich syndrome, are recognized causes of IO colitis.

In the present study on six Asian children with IO-IBD, the disease phenotype was diverse. From the initial presentation and subsequent disease course, three patients [1 UC (patient No. 2) and 2 CD (patient No. 4 and 5)] closely resembled classical UC and CD. In the remaining three cases, the disease behavior and progression significantly differed from classical CD or UC.

The only patient with IBD-U achieved sustained remission and resolution of the perianal disease after ileostomy was created at four months of age, despite no immunosuppression. The initial features were indistinguishable with that of classical CD with severe perianal abscesses and fistulas, and the presence of deep, linear, extensive ulcerations at the rectum and sigmoid colon. Severe allergic colitis was unlikely as the initial histology showed transmural involvement. There was continuing remission even after the closure of ileostomy at 16 mo of age. Mutational analysis for *IL10* and *IL10R* was negative.

A review in the literature did not reveal any cases of CD with spontaneous remission without immunosuppression or other medical therapy[31,32]. Thus even though the clinical, colonoscopic and histological features in this patient closely resembled that of CD, the child was classified as having IBD-U.

Another interesting case that merits special attention was the child with initial presentation with pancolitis, heavy eosinophilic infiltration of the colonic mucosa,

and resistance to elemental formula and even immunosuppression. This closely resembled a case of severe allergic colitis. This was followed at later stage with lymphoplasmacytic infiltration seen typically in IBD. This transformation from allergic colitis to IBD has been similarly observed by other authors[8].

Our findings are similar to those described by other authors[8,9,14]. Generally, patients with IO-IBD need aggressive therapy, often with a combination of immunosuppression[8,9,14]. Some needed biologics such as IFX[9]. Between 19% to 33% needed surgery, either ileostomy or colectomy[8,9]. Nevertheless complete remission can be achieved in a significant proportion of patients either with ongoing immunosuppression or discontinuation of therapy[8,9,14].

With the exception that children with IO-IBD were more likely to have bloody diarrhea at presentation, there were no significant differences between the IO-IBD and children with the onset of disease after one-year of age in terms of developing autoimmune liver disease, the need for biologics, risk for subsequent surgery, achieving remission at final review, or achieving remission without on-going immunosuppression.

Unlike the authors from Korea which showed that 50% of the 14 children with IO-IBD had mutations in IL10RA[19], none of the three patients with CD phenotype and the case with IBD-U in the present study had any identified mutations in *IL10* or *IL10R*. Nevertheless continuing efforts is necessary to identify such mutations in all patients with IO-IBD. However, it should be pointed out that only four of the six patients with IO-IBD had mutational analysis for *IL10* and *IL10R* performed. The remaining two patients, who both had phenotype similar to UC, had no mutational analysis. This was because IO-IBD secondary to mutations in *IL10* and *IL10R* genes usually present with CD phenotype.

The present study was conducted from a region where the incidence of IBD is much lower as compared to the West[33]. This have contributed to the small number of patients with both IO-IBD and later-onset disease reported in the present study.

We did not perform anti-*Saccharomyces* cerevisae antibody (ASCA) for the patients with early onset disease. Recently, high ASCA seropositivity rates have been found in patients with early-onset IBD[34]. The implications of finding a positive ASCA in patient with CD include oral involvement and a more severe disease[35]. However, the finding of high seropositivity rate of ASCA in early onset CD has not been reported by other authors[36].

There are several weaknesses in the present study. Firstly, the number of children with infantile colitis described was small. The present study was conducted in an area with low incidence of IBD. Over the study period of 18 years in the only referral center for pediatric IBD in Malaysia, only six cases of IO-IBD were noted. Thus it may be difficult to draw many significant conclusions from the findings of the present study.

Secondly, mutational analysis for other known causes of infantile colitis were not performed in the six cases of IO-IBD described in the present study[10]. Thus we were unable to characterize further the genetic basis of these six cases of IO-IBD described.

In addition, there may be selection bias when comparing the outcome of IO-IBD with the outcome of patients with later-onset disease. It is well known that IO-IBD is a heterogenous group of conditions and is comprised of several different disease caused different genetic mutations but characterized by early onset of disease.

However, it is well known that the incidence of IBD in Asian adults is increasing[33]. It is anticipated that the incidence of IBD in Asian children would similarly be increasing[33]. The present study will add to the body of knowledge for this rare disease in Asian children. Currently, most of the cases of IO-IBD described in the literature were from the Middle East or Caucasian population[8,9].

We conclude that IO-IBD consists of a heterogeneous group of disorders with different pathogenic mechanisms but with the common manifestation of severe colitis presenting in the first few months of life. Aggressive immunosuppression and surgery are often necessary. Nevertheless sustained remission, in some cases without immunosuppression, can be achieved in a significant proportion of patients. Continuing efforts to elucidate novel mechanisms responsible for the breaking down of intestinal integrity is necessary in this group of infants.

ACKNOWLEDGMENTS

The present research was funded by a research grant from Ministry of Higher Education, Malaysia (UM.C/625/HIR/MOHE/CHAN/13/1). None of the authors declared any potential conflict of interest. The genetics study of patients with primary immunodeficiencies was funded by the Hong Kong Society for the Relief of Disabled Children.

COMMENTS

Background

Inflammatory bowel disease (IBD) is not as common in the Asian population as in the Caucasians, although recent epidemiology studies suggest that the incidence of IBD in the Asian population is increasing. Infantile-onset inflammatory bowel disease (IO-IBD) is uncommon and is usually associated with a genetic mutation. One of the most common mutations described that is associated with IO-IBD is mutations in IL-10 and IL-10 receptor.

Research frontiers

It is important to elucidate the role of IL-10 and *IL-10* mutations in children with IO-IBD as it is usually non-responsive to conventional immunosuppressive therapy but may be amendable to stem-cell transplantation.

Innovations and breakthrough

As compared to children with IBD with an onset after the first year of life, IO-IBD achieved remission at a similar rate, were more likely to discontinue immunosuppression therapy while not more likely to require biologics therapy or surgical intervention.

Applications

Although mutations in *IL-10* and *IL-10R* were not found in the present cohort of infantile-onset inflammatory bowel disease, it is important to screen for such mutations in all cases of IO-IBD as the therapy and prognosis is different.

Terminology

IO-IBD refers to a subset of early-onset IBD with an onset before twelve months of life.

Peer-review

The manuscript is interesting and adds new knowledge in the field of IO-IBD but requires a major statistical revision (or no statistical analysis as the conclusions may be false and can not be extrapolated on the bigger group of all IO-IBD patients).

REFERENCES

1 **Kappelman MD**, Grand RJ. Does inflammatory bowel disease develop in infants? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S6-S8 [PMID: 18816729 DOI: 10.1002/ibd.20544]

2 **Gower-Rousseau C**, Salomez JL, Dupas JL, Marti R, Nuttens MC, Votte A, Lemahieu M, Lemaire B, Colombel JF, Cortot A. Incidence of inflammatory bowel disease in northern France (1988-1990). *Gut* 1994; **35**: 1433-1438 [PMID: 7959201]

3 **Miralles R**, Santander H, Ide W, Bull R. Influence of mucosal mechanoreceptors on elevator muscle activity in healthy subjects. *J Prosthet Dent* 1991; **65**: 431-435 [PMID: 2056465 DOI: 10.1002/ibd.21349]

4 **Oliva-Hemker M**, Hutfless S, Al Kazzi ES, Lerer T, Mack D, LeLeiko N, Griffiths A, Cabrera J, Otley A, Rick J, Bousvaros A, Rosh J, Grossman A, Saeed S, Kay M, Carvalho R, Keljo D, Pfefferkorn M, Faubion W, Kappelman M, Sudel B, Schaefer ME, Markowitz J, Hyams JS. Clinical Presentation and Five-Year Therapeutic Management of Very Early-Onset Inflammatory Bowel Disease in a Large North American Cohort. *J Pediatr* 2015; **167**: 527-532.e1-3 [PMID: 25982142 DOI: 10.1016/j.jpeds.2015.04.045]

5 **Kugathasan S**, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, Weisdorf-Schindele S, San Pablo W, Perrault J, Park R, Yaffe M, Brown C, Rivera-Bennett MT, Halabi I, Martinez A, Blank E, Werlin SL, Rudolph CD, Binion DG. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003; **143**: 525-531 [PMID: 14571234]

6 **Hildebrand H**, Finkel Y, Grahnquist L, Lindholm J, Ekbom A, Askling J. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990-2001. *Gut* 2003; **52**: 1432-1434 [PMID: 12970135]

7 **Heyman MB**, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, Winter HS, Fain P, King C, Smith T, El-Serag HB. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005; **146**: 35-40 [PMID: 15644819]

8 **Ruemmele FM**, El Khoury MG, Talbotec C, Maurage C, Mougenot JF, Schmitz J, Goulet O. Characteristics of inflammatory bowel disease with onset during the first year of life. *J Pediatr Gastroenterol Nutr* 2006; **43**: 603-609 [PMID: 17130735]

9 **Cannioto Z**, Berti I, Martelossi S, Bruno I, Giurici N, Crovella S, Ventura A. IBD and IBD mimicking enterocolitis in children younger than 2 years of age. *Eur J Pediatr* 2009; **168**: 149-155 [PMID: 18546019]

10 **Uhlig HH**. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. *Gut* 2013; **62**: 1795-1805 [PMID: 24203055 DOI: 10.1136/gutjnl-2012-303956]

11 **Glocker EO**, Frede N, Perro M, Sebire N, Elawad M, Shah N, Grimbacher B. Infant colitis--it's in the genes. *Lancet* 2010; **376**: 1272 [PMID: 20934598 DOI: 10.1016/S0140-6736(10)61008-2]

12 **Soubiran JM**. [Decubitus ulcer. General conclusions]. *Soins* 1979; **24**: 43 [PMID: 256647 DOI: 10.1097/DCR.0000000000000274]

13 **Uhlig HH**, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, Ouahed J, Wilson DC, Travis SP, Turner D, Klein C, Snapper SB, Muise AM. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014; **147**: 990-1007.e3 [PMID: 25058236 DOI: 10.1053/j.gastro.2014.07.023]

14 **Glocker EO**, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, Perro M, Diestelhorst J, Allroth A, Murugan D, Hätscher N, Pfeifer D, Sykora KW, Sauer M, Kreipe H, Lacher M, Nustede R, Woellner C, Baumann U, Salzer U, Koletzko S, Shah N, Segal AW, Sauerbrey A, Buderus S, Snapper SB, Grimbacher B, Klein C. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009; **361**: 2033-2045 [PMID: 19890111 DOI: 10.1056/NEJMoa0907206]

15 **Begue B**, Verdier J, Rieux-Laucat F, Goulet O, Morali A, Canioni D, Hugot JP, Daussy C, Verkarre V, Pigneur B, Fischer A, Klein C, Cerf-Bensussan N, Ruemmele FM. Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. *Am J Gastroenterol* 2011; **106**: 1544-1555 [PMID: 21519361 DOI: 10.1038/ajg.2011.112]

16 **Kotlarz D**, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, Pfeifer D, Kreipe H, Pfister ED, Baumann U, Puchalka J, Bohne J, Egritas O, Dalgic B, Kolho KL, Sauerbrey A, Buderus S, Güngör T, Enninger A, Koda YK, Guariso G, Weiss B, Corbacioglu S, Socha P, Uslu N, Metin A, Wahbeh GT, Husain K, Ramadan D, Al-Herz W, Grimbacher B, Sauer M, Sykora KW, Koletzko S, Klein C. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy.*Gastroenterology* 2012; **143**: 347-355 [PMID: 22549091 DOI: 10.1053/j.gastro.2012.04.045]

17 **Pigneur B**, Escher J, Elawad M, Lima R, Buderus S, Kierkus J, Guariso G, Canioni D, Lambot K, Talbotec C, Shah N, Begue B, Rieux-Laucat F, Goulet O, Cerf-Bensussan N, Neven B, Ruemmele FM. Phenotypic characterization of very early-onset IBD due to mutations in the IL10, IL10 receptor alpha or beta gene: a survey of the Genius Working Group. *Inflamm Bowel Dis* 2013; **19**: 2820-2828 [PMID: 24216686 DOI: 10.1097/01.MIB.0000435439.22484.d3]

18 **Dinwiddie DL**, Bracken JM, Bass JA, Christenson K, Soden SE, Saunders CJ, Miller NA, Singh V, Zwick DL, Roberts CC, Dalal J, Kingsmore SF. Molecular diagnosis of infantile onset inflammatory bowel disease by exome sequencing. *Genomics* 2013; **102**: 442-447 [PMID: 24001973 DOI: 10.1016/j.ygeno.2013.08.008]

19 **Engelhardt KR**, Grimbacher B. IL-10 in humans: lessons from the gut, IL-10/IL-10 receptor deficiencies, and IL-10 polymorphisms. *Curr Top Microbiol Immunol* 2014; **380**: 1-18 [PMID: 25004811 DOI: 10.1007/978-3-662-43492-5_1]

20 **Prideaux L**, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. *J Gastroenterol Hepatol* 2012; **27**: 1266-1280 [PMID: 22497584 DOI: 10.1111/j.1440-1746.2012.07150.x]

21 **Mao H**, Yang W, Lee PP, Ho MH, Yang J, Zeng S, Chong CY, Lee TL, Tu W, Lau YL. Exome sequencing identifies novel compound heterozygous mutations of IL-10 receptor 1 in neonatal-onset Crohn's disease. *Genes Immun* 2012; **13**: 437-442 [PMID: 22476154 DOI: 10.1038/gene.2012.8]

22 **Shim JO**, Seo JK. Very early-onset inflammatory bowel disease (IBD) in infancy is a different disease entity from adult-onset IBD; one form of interleukin-10 receptor mutations. *J Hum Genet* 2014; **59**: 337-341 [PMID: 24785691 DOI: 10.1038/jhg.2014.32]

23 **Levine A**, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, Kolho KL, Veres G, Russell RK, Paerregaard A, Buderus S, Greer ML, Dias JA, Veereman-Wauters G, Lionetti P, Sladek M, Martin de Carpi J, Staiano A, Ruemmele FM, Wilson DC. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014; **58**: 795-806 [PMID: 24231644 DOI: 10.1097/MPG.0000000000000239]

24 **Levine A**, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, Fell J, Ruemmele FM, Walters T, Sherlock M, Dubinsky M, Hyams JS. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011; **17**: 1314-1321 [PMID: 21560194 DOI: 10.1002/ibd.21493]

25 **Kammermeier J**, Morris MA, Garrick V, Furman M, Rodrigues A, Russell RK. Management of Crohn's disease. *Arch Dis Child* 2016; **101**: 475-480 [PMID: 26553907 DOI: 10.1136/archdischild-2014-307217]

26 **Nolte T**. Stfm launches interprofessional leading change fellowship. *Ann Fam Med* 2015; **13**: 593 [PMID: 26553903 DOI: 10.1136/archdischild-2014-307218]

27 **Hyams JS**, Griffiths A, Markowitz J, Baldassano RN, Faubion WA, Colletti RB, Dubinsky M, Kierkus J, Rosh J, Wang Y, Huang B, Bittle B, Marshall M, Lazar A. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012; **143**: 365-374.e2 [PMID: 22562021 DOI: 10.1053/j.gastro.2012.04.046]

28 **Hyams JS**, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, Griffiths AM, Katz AJ, Grand RJ, Boyle JT. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991; **12**: 439-447 [PMID: 1678008]

29 **Turner D**, Hyams J, Markowitz J, Lerer T, Mack DR, Evans J, Pfefferkorn M, Rosh J, Kay M, Crandall W, Keljo D, Otley AR, Kugathasan S, Carvalho R, Oliva-Hemker M, Langton C, Mamula P, Bousvaros A, LeLeiko N, Griffiths AM. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis* 2009; **15**: 1218-1223 [PMID: 19161178 DOI: 10.1002/ibd.20867]

30 **Turner D**, Levine A, Kolho KL, Shaoul R, Ledder O. Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report. *J Crohns Colitis* 2014; **8**: 1464-1470 [PMID: 24958064 DOI: 10.1016/j.crohns.2014.05.010]

31 **Hoption Cann SA**, van Netten JP. Spontaneous remission of Crohn's disease following a febrile infection: case report and literature review. *BMC Gastroenterol* 2011; **11**: 57 [PMID: 21592411 DOI: 10.1186/1471-230X-11-57]

32 **Short SS**, Dubinsky MC, Rabizadeh S, Farrior S, Berel D, Frykman PK. Distinct phenotypes of children with perianal perforating Crohn's disease. *J Pediatr Surg* 2013; **48**: 1301-1305 [PMID: 23845622 DOI: 10.1016/j.jpedsurg.2013.03.027]

33 **Ng SC**, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeena MN, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJ, Chan FK. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013; **145**: 158-165.e2 [PMID: 23583432 DOI: 10.1053/j.gastro.2013.04.007]

34 **Nisihara RM**, de Carvalho WB, Utiyama SR, Amarante H, Baptista ML. Diagnostic role and clinical association of ASCA and ANCA in Brazilian patients with inflammatory bowel disease. *Dig Dis Sci* 2010; **55**: 2309-2315 [PMID: 19826949 DOI: 10.1007/s10620-009-0998-7]

35 **Bueno de Mesquita M**, Ferrante M, Henckaerts L, Joossens M, Janssens V, Hlavaty T, Pierik M, Joossens S, Van Schuerbeek N, Van Assche G, Rutgeerts P, Vermeire S, Hoffman I. Clustering of (auto)immune diseases with early-onset and complicated inflammatory bowel disease. *Eur J Pediatr* 2009; **168**: 575-583 [PMID: 18670786 DOI: 10.1007/s00431-008-0798-7]

36 **Mamula P**, Telega GW, Markowitz JE, Brown KA, Russo PA, Piccoli DA, Baldassano RN. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol* 2002; **97**: 2005-2010 [PMID: 12190168 DOI: 10.1111/j.1572-0241.2002.05915.x]

P- Reviewer: Koh SJ, Takagi T, Waszczuk K **S- Editor**: Yu J
L- Editor: A **E- Editor**: Zhang FF

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327