RESEARCH BRIEF

Age-related Differences in the Clinical Course of Crohn's Disease in an Asian Population: A Retrospective Cohort Review

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The aim of this study was to compare the clinical characteristics and treatment outcomes of patients with young- and adult-onset Crohn's disease. Among 79 consecutive Crohn's disease patients (11 (13.92%) with onset ≤16 years old), young-onset Crohn's disease was significantly associated with fever(36.36 vs. 14.71%, *P* 0.041), weight loss (72.7 vs. 29.4%, *P* 0.003), isolated abdominal pain (45.45 vs. 16.18%, *P* 0.013), lower body mass index (17.32 vs. 21.29 kg/m^2, *P* 0.019), and extra-intestinal manifestation, particularly oral (45.5% vs. 22.1%, *P* 0.049) and perianal lesion (63.6% vs. 36.8%, *P* 0.046). In both groups, ileocolonic disease and inflammatory lesion were the most prevalent site of involvement and dominant disease behavior respectively. Their complication and bowel resection rate were similar but the former took a longer period of time to develop in the young-onset group (84 *vs* 24 month, *P* 0.018). Cox proportional hazard regression analysis revealed that active smoking and delayed use of immuno-suppressive therapy were the only independent risk factors associated with increased risk of complications.

Key words: *Asian population, Crohn's disease, Young-onset.*

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Previous reports have suggested that young-onset Crohn's disease has several clinical features that are distinct from those in adults and it might have a relatively more complicated clinical course due to associated growth and developmental problems [1-3]. However, most studies came from the Western countries and they did not include adult patients for comparison [4]. Data from Asian populations about young-onset Crohn's disease are few, particularly risk factors predicting the development of complications during the clinical course among different age groups [5].

In the current study, we sought to assess clinical presentation, phenotypes according to the Montreal classification and potential risk factors for complications in patients with young-onset Crohn's disease.

METHOD

Patient population: The study population consisted of 79 consecutive patients with Crohn's disease treated in Tuen Mun Hospital(TMH) of Hong Kong from Jan 2000 to Dec 2012. The diagnosis of Crohn's disease was based on clinical, ileocolonoscopic, histopathologic, and radiologic findings [6]. Single-balloon enteroscopy, capsule endoscopy, fluoroscopy or both was performed when disease of the small intestine was suspected. Crohn's disease was classified according to the Montreal classification [6]. Throughout this study, young-onset was defined as individual aged ≤16 years for onset of Crohn's disease. The disease location was determined at diagnosis and its behavior was categorized during follow-up.

Data collection: The clinical records of these patients were retrospectively reviewed to obtain:

(*i*) Demographic characteristics including gender, smoking habits and body mass index(BMI) on presentation,

(*ii*) Symptoms at onset and significant findings on physical examination

(*iii*) Laboratory parameters, such as hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein and serum albumin, and disease activity indices (Pediatric Crohn's Disease Activity Index[PCDAI] and Crohn's disease Activity Index [CDAI] in young-onset and adult-onset group respectively) on initial presentation,

(*iv*) Prescription of 5-aminosalicylic acid compounds, immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), and biologics such as monoclonal antibody against tumor necrosis factor α (anti-TNF α)

(*v*) Complications including surgical intervention

Statistical analysis: The data were compiled and analyzed by use of the commercial Statistical Package for the Social Sciences (SPSS) for Window (version17.0; SPSS Inc, Chicago, IL). All continuous variables were expressed as median and interquartile range(IQR). Categorical variables

TABLE I DEMOGRAPHIC, CLINICAL AND PHENOTYPIC CHARACTERISTICS OF PATIENTS WITH CROHN'S DISEASE

Variable	*Young onset (n=11)*	*Adult onset (n=68)*	*P value*
Sex, male: female	8:3	47:21	0.405
Duration of symptoms before presentation, median week (IQR)	17.2 (48)	12 (22)	0.348
Body mass index (kg/m^2)	17.32 (9.28)[1]	21.29 (5.5)	0.019
Fever	4 (36.36)	10 (14.71)	0.041
Weight loss	8 (72.7%)[2]	20 (29.4%)	0.003
Gastrointestinal manifestation			
Abdominal pain	11 (100%)	55 (80.9%)	0.056
Only presenting symptom	5 (45.45%)	11 (16.18%)[3]	0.013
Peri-rectal bleeding	5 (45.5%)	32 (47.1%)[4]	0.460
Diarrhoea	4 (36.4%)	37 (54.4%)	0.136
Others	0 (0%)	16 (23.5%)[5]	0.036
Extra-intestinal manifestation			
Oral aphthous ulcers/stomatitis	5 (45.5%)	15 (22.1%)	0.049
Polyarthralgia	2 (18.2%)	9 (13.2%)	0.330
Others	2 (18.2%)[6]	3 (4.41%)[7]	0.041
Phenotypic characteristics[8]			
L1/L2/L3	1 (9.1%)/	11 (16.2%)/	0.271
	3 (27.3%)/	23 (33.8%)/	0.336
	6 (54.5%)	32 (47.1%)	0.323
L4 [9]	3 (27.3%)	7 (10.3%)	0.057
B1/2/3	7 (63.6%)/	39 (57.4%)/	0.352
	2 (18.2%)/	9 (13.2%)/	0.330
	2 (18.2%)	20 (29.4%)	0.159
Perianal lesions	7(63.6%)	25 (36.8%)	0.046
Skin tag/fistula/abscess	1/3/3	4/13/8	
Laboratory parameters			
Hemoglobin (g/dL)	11 (2)	12.5 (3.5)	0.152
Albumin (g/L)	36 (8)	38 (8.5)	0.391
Erythrocyte sedimentation rate(mm/hr)	64 (48)	38 (35.5)	0.13
C-reactive protein(mg/L)	52 (35.4)	20.5 (38.25)	0.011

Note. Data are either median (IQR) or no. (%) of patients, unless otherwise indicated. Boldface type indicates statistical significance.[1]: Failure to thrive(n=5), body height below 5th percentile(n=4)[2]: below the third percentile of the mean(n=5) [3]: acute pain with rebound tenderness(n=7)[4]: hemodynamic instability (n=5) [5]: right lower quadrate mass (n= 6), peritonitis (n=5), intestinal obstruction (n=5)[6]: erythema nodosum (n=1), uveitis (n=1) [7]: pyoderma gangrenousm (n=1),uveitis(n=1),primary sclerosing cholangitis (n=1) [8]: A2, n=47(69.1%); A3, 21(30.9%) [9]: isolated L4 , Young (n=1), Adult(n=2)

were reported as percent. The chi-square test, Fisher's exact test and Mann-Whitney U test were used when appropriate. The Kaplan-Meier method was used to estimate the cumulative complication rate of the two groups of patients, and the log-rank test was used to test for statistical significance. Multivariate Cox proportional hazards regression analysis was performed to identify independent risk factors for development of complications. Effects of potential risk factors (namely age ≤16 years old, male sex, smoking history, ileocolonic disease location, upper gastrointestinal [GI] tract involvement, presence of perianal lesions, ≥12 months on delayed use of immunosuppressive therapy, surgery on initial presentation) were quantified by calculating the hazard ratio (HR) and confidence interval (CI) from the final Cox model. *P* value less than .05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics: Among 79 patients with Crohn's disease diagnosed in TMH, 11 (13.92%) of them had disease onset with age ≤16 year old

(range: from 11 to 16 year old). Median age at onset of symptoms was 13 years (IQR, 4 years) versus 29 years (IQR, 19 years) in the young and adult-onset group, respectively and there was no significant difference between their median follow-up periods (8 years (IQR, 5 years) *vs* 7 years (IQR, 9 years), *P*=0.884). In this cohort, only two (2(2.9%) *vs* 0(0%), *P* 0.281) and nineteen (19 (27.9%) *vs* 0(0%), *P* 0.023) patients from the adult-onset group had family history of Crohn's disease and active smoking history before the disease onset. One young-onset patient received empirically a course of anti-tuberculous therapy before making the diagnosis of Crohn's disease. Young-onset patients tended to have upper GI tract involvement (L4) in which among them, these lesions were as follows: one case with an isolated ileal stricture demonstrated in small bowel barium enema examination, one case with granulomatous inflammation in duodenal and jejunal mucosa revealed in upper endoscopic examination and another case presented with acute abdomen with sign of intestinal obstruction with an isolated granulomatous inflammatory mass lesion at small bowel revealed in an exploratory laparotomy. Oesophagogastroduodenoscopy (OGD) with histo-pathological assessment of antral biopsy performed in another four young-onset patients did not revealed any abnormality. In the adult group, twenty-seven of them had OGD performed and the lesions were as follows: two cases with non-*Helicobacter pylori (HP)* associated duodenal ulceration and two cases each with HP associated gastric ulceration and antral gastritis.

Among the young – onset patients, median PCDAI at which the diagnosis of Crohn's disease was established was 30 (IQR, 12.5) in which four (36.36%) of them were in moderate-to-severe disease activity (*i.e.* PCDAI >30); while in the adult-onset group, median CDAI was 119 (IQR, 62.5) in which none of them were in moderate or above in severity and only 16 (23.53%) of them were in mild activity (*i.e.* CDAI:150-219) .

Treatment and outcomes: Overall, only 8 (10.1%) patients had history of anti-TNFá exposure during the study period in which it primarily acted as maintenance and rescue therapy in the young- and adult-onset patients respectively. Despite maximum dosage of immunosuppressive agents, two (18.18%) young-onset patients at age of 21 and 23 years old (*i.e.* 6 and 9 years of illness respectively) required the anti-TNFα maintenance therapy to control the disease activity. Of the two cases on infliximab, lack of response was noted in one patient two years after therapy and it was switched over to adalimumab with which remission was attained and sustained for next five years. Though the complication rates were similar between the two groups, it took significantly a longer period of time (84 *vs* 24 month, *P* 0.018) to develop in the young-onset group. The main complications were bowel perforation and progressive stricturing Crohn's disease causing intestinal obstruction. Regarding the obstructive Crohn's strictures in the young-onset group, they were two cases of ileal, one case each of ascending and descending colonic stricture. On the other hand, there are eighteen obstructive strictures among the adult-onset patients with their locations as follows: four cases each of anastomosis and ileum, three cases of descending colon, two cases each of small intestine, ileocecal region and ascending colon; and one case of rectum. Seven (10.29%) of the adult-onset group had bowel perforation due to progressive penetrating disease behavior

TABLE II MANAGEMENT AND CLINICAL OUTCOMES OF PATIENTS WITH CROHN'S DISEASE

Management	*Young onset(n=11)*	*Adult onset (n=68)*	*P value*
Medical therapy			
Oral 5-aminosalicylic acid	7(63.63%)	68(100%)	0.000
Immunosuppressive therapy [1]	9(81.8%)	52 (76.5%)	0.348
Time(month, IQR) required to start	38.22(42.74)	20.43(25.42)	0.232
Side effect (*n*, %)	1(9.1)[2]	9(13.23)[3]	0.352
Anti-TNF α	2(18.18%)[4]	6(8.82%)[5]	0.169
Complications (*n*, %)	5(45.5%)	29(42.6%)	0.429
Median time(month,IQR) to develop	84(141)	24(77)	0.018
Bowel stricture	4	18	
Others	1[6]	11[7]	
Bowel resection (*n*,%)	3(27.3%)	19(28.1%)	0.480

Data are no. (%) of patients, unless otherwise indicated. Boldface type indicates statistical significance.[1]: all cases were AZA except : MTX (n=1) in young-onset , 6-MP (n=3) and MTX (n=2) in adult group. [2]:MTX induced hepatitis[3]: reversible bone marrow suppression (n=5), hepatitis (n=2) and cutaneous rash (n=1) by AZA, MTX induced Pneumocystis pneumonia (n=1) [4]: maintenance therapy with infliximab (n=1) and adalimumab (n=1) [5]: rescue therapy for active disease (n=5) and closure of fistula-in-ano (n=1). [6]: abdominal abscess (n=1) [7]:bowel perforation(n=7), abdominopelvic abscess(n=2),severe gastrointetinal bleeding (n=12) 6-mercaptopurine (6-MP), azathioprine (AZA), methotrexate (MTX).

WHAT THIS STUDY ADDS?

- Young-onset Crohn's disease has distinct clinical features as compared adult-onset type but it does not carry higher risk of complications.

whereas no bowel perforation was reported in the young-onset group.

All three cases in the young-onset group with bowel resection presented acutely with emergent operations performed and they are as follows: ileal inflammatory mass causing intestinal obstruction required small bowel resection, two cases required right hemicolectomy with indication of right lower quadrant tenderness with peritonitis and toxic mega-colon. Among the adult-onset patients, three cases had obstructive small bowel disease treated with surgical resection and the causes of intestinal obstruction included progressive ileal stricture, inflammatory mass lesion of small intestine causing intussusception and bezoar obstruction respectively. The other sixteen patients in the adult-onset group had hemi-colectomy performed with indications including penetrating disease causing bowel perforations in twelve cases in which nine of them were complicated with abdominal abscess, stricturing disease behavior resulting colonic obstruction and profuse lower gastrointestinal bleeding in two cases respectively.

Kaplan-Meier analysis showed that the cumulative rate of complications over the disease course was statistically significant difference (Log rank test, *P* 0.035) between the two groups. After eliminating effect of confounding variables, Cox proportional hazard regression analysis revealed that active smoking (hazard ratio[HR], 4.68; 95% confidence interval [CI]:1.03-4.09; *P* 0.045) and delayed use of immuno-suppressive therapy (HR, 4.13; 95% CI: 1.01-16.88; *P* 0.048) were the only independent risk factors associated with increased risk of complications while age at diagnosis did not reach a significant level in the multi-variate model (HR, 0.47; 95% CI: 0.13-1.66; *P* 0.24).

DISCUSSION

This study revealed that young-onset Crohn's disease had distinct clinical features as compared with adult-onset type, particularly abdominal pain ,fever and weight loss as an important triad of symptoms in the young-onset ;but there were no significant difference in the complication and bowel resection rate between the two groups.

The distinct clinical profiles of the two groups might be due to differential impact of lengthy duration of presenting symptoms according to their age of presentation [3]. In young patients, this would cause progressive weight loss, low BMI and growth failure via the long standing effect of chronic illness and malabsorption while in the adult-onset, this, due to their poor awareness of the illness, resulted in considerable amount of patients presented acutely, such as severe lower GI bleeding, peritonitis and intestinal obstruction. The higher prevalence of oral manifestation in the pediatric group might be accounted by the indirect effect of Crohn's disease via malabsorption. In congruent with the previous Asian studies, ileo-colonic disease was the most common disease location [2,4,7-10]. In our study, we highlighted two distinct phenotypic characteristics in the pediatric group. Firstly, the frequency of upper GI disease was higher than that of the adult group [11]. This is explained by fluoroscopic examination of upper GI tract more widely performed in our pediatric cohort. Secondly, perianal lesion was also found more frequently. In fact, the higher proportion of upper GI and perianal involvement in pediatric patients was also observed in the other Asian studies [4,11,12].

Previous studies reported that Crohn's disease runs a more aggressive course in young population and the underlying reason might be related to the evolution from inflammatory behavior to a more complicated behavior (stricturing or penetrating) which is well demonstrated in the Western literatures as well as another Hong Kong study [10,13]. However, this association was failed to demonstrate in our cohort. Instead, there was significant delay in complication development in the pediatric group. This might be related to more widely use of immuno-suppressive therapy in our pediatric group. In our study, only smoking and delay use of immunosuppressive therapy were found to be significantly associated with complication development.

This study enables us to better understand the characteristics of young-onset Crohn's disease and provide better clinical care for them. The limitations of this study are its retrospective design and single-centre data.

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