

# A Retrospective Study on Clinical Characteristics of Paediatric Crohn's Disease

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## Abstract

**Objectives:** The aim of this study is mainly to describe the clinical pattern of paediatric Crohn's disease (CD) and improve diagnostic accuracy and therapeutic efficacy. **Methods:** CD patients between the ages of 0 and 18 years old were identified by survey of computerised medical information. Twenty cases were selected for this retrospective study. **Results:** The median age at diagnosis was 9.4 years (range, 25 days-17 years). The peak prevalence of CD was observed in the 10-14 years old age group. Sixty (50%) were males. All the children are Han Chinese ethnicity. The most common presenting symptoms was diarrhoea (70%), fever (60%), abdominal pain (55%) and bloody stool (10%). At least one extra-intestinal manifestations occurred in 35% of Crohn's disease patients. Growth retardation is another common complication, which is presented in 50% of patients. The most common distribution were ileo-colon (45%) and colon (35%). Perianal disease also occurred in 25% children with CD. According to the laboratory findings, anaemia presented in 70% patients, thrombocytosis presented in 70% and hypoalbuminaemia presented in 65%. Three patients underwent the surgery, after which death was caused in 2 cases. **Conclusion:** The clinical features of paediatric Crohn's disease are found to be complicated and nonspecific. Recognition of CD by paediatricians is necessary for proper diagnosis and management.

## Key words

China; Crohn's disease; Paediatric

## Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic diseases related to a mucosal immune response to antigenic stimulation from the gut microbiota. CD is a chronic granulomatous inflammation affecting any part of the gastrointestinal tract from mouth to anus, with discontinuity in affected areas.

The cause remains unknown. CD has been regarded as a disease primarily occurring in Western populations. It was thought that CD was rare or nonexistent in China. There are reports of an increase in CD among children.<sup>1</sup> The clinical symptoms of CD in Children are indicated to be more complicated and nonspecific than in adults, which often takes a greater physical and emotional toll on children and adolescents. Because of limited epidemiologic data, the true burden of CD in Chinese children is difficult to estimate. Our retrospective study on hospitalised children patients with CD in 20 cases is expected to provide some experience and suggestions for proper diagnosis and management of the disease.

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## Patients and Methods

We identified 20 hospitalisation cases with Crohn's disease in Yuying Children's Hospital affiliated to Wenzhou Medical University, China from January 2000 to January

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2013. The diagnosis was made, based on the symptoms, colonoscopy (capsule endoscopy only for patients with small bowel lesions), barium enema, mucosal biopsy, which are considered as the diagnostic "golden standard" by Chinese Society of Gastroenterology. Three pathologically confirmed cases of CD were treated surgically. Colonic infections were excluded by repeated stool examination and culture. Tuberculosis was excluded on the basis of purified protein derivative test result. Disease distribution were analysed according to the Montreal Classification<sup>2</sup> where L1 stands for ileal, L2 for colonic, L3 for ileo-colonic, and L4 for disease in the upper gastrointestinal tract. Growth retardation was defined in the following ways: (1) by a static measurement of height/weight below the third percentile; (2) by evidence of significant growth change as assessed over time by percentile chart analysis; and (3) by showing a reduction in height velocity  $<-2.0$  standard-deviation scores.<sup>3</sup> In all selected cases, the patients' general information (age, sex, family history etc.), symptoms, assistant examinations, therapy were reviewed.

## Results

### General Data

We analysed 20 hospitalisation cases (12 male patients and 8 female patients; gender ration, 1.5:1) from Department of Pediatric Internal Medicine, Department of Pediatric Surgery and Department of Colorectal Surgery from January 2000 to January 2013. Mean age at diagnosis was 9.4 years (range: 25 days-17 years); all the patients were divided into 4 different age groups: 0-4 years (4), 5-9 years (4), 10-14 years (8), 15-18 years (4). The age distribution is shown in Figure 1. Duration from disease onset to diagnosis ranged from 1 month to 9 years (34 months in average). All the children are Han Chinese ethnicity and no family history was reported.

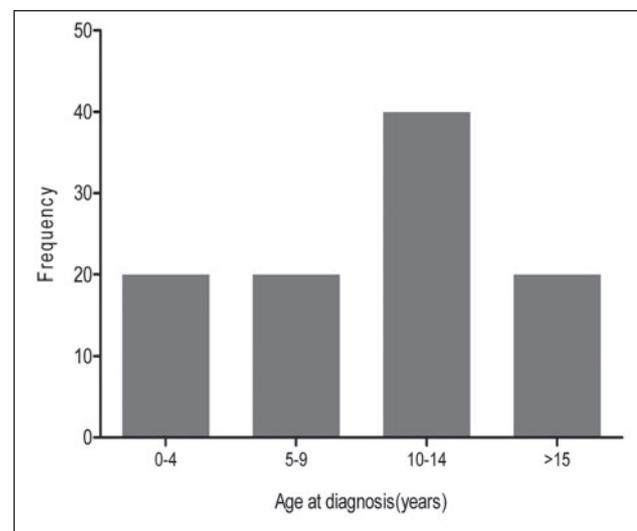
### Clinical Symptoms

The clinical symptoms of paediatric Crohn's disease were shown in Table 1. The main symptoms at diagnosis include: diarrhoea (70%), fever (60%), abdominal pain (55%) and bloody stool (10%). Five patients presented with perianal disease (1 with perianal abscess, 4 with anal fistula), in which 2 cases of perianal disease occurred prior to gastrointestinal diseases. Seven patients of all presented with extra-intestinal manifestations, 6 with oral ulcer, 1 with perineal ulcer and 1 with rash.

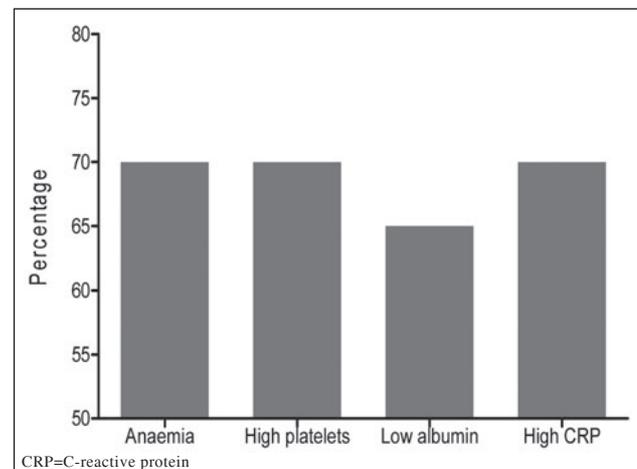
Table 2 shows the distribution and behaviour of CD patients based on the Montreal Classification at diagnosis. The most common location of CD patients were ileo-colon (45%) and colon (35%), and the upper gastrointestinal tract was involved in 5 cases. Strictures were identified in 4 (20%) patients. Penetrating complications occurred in 6 (30%) patients. Inflammatory (non-stricturing and non-penetrating) disease was found in 10 cases.

### Laboratory Findings

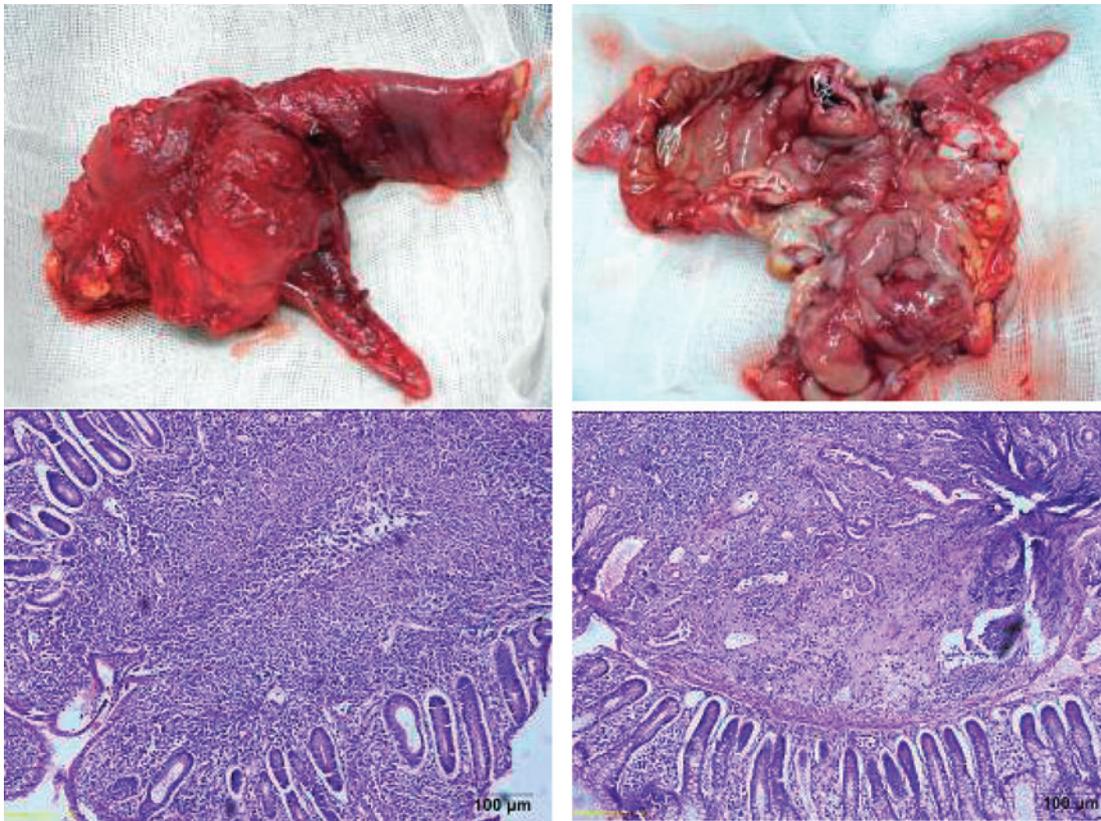
The laboratory findings indicated that 70% of patients had anaemia and the mean $\pm$ SD haemoglobin level showed as  $97\pm 16$  g/L (normal: 120~160 g/L), 70% had thrombocytosis with a mean $\pm$ SD platelet count of



**Figure 1** The age distribution at the time of Crohn's disease diagnosis (n=20).



**Figure 2** Laboratory results.



**Figure 3** Pathological diagnosis.

**Table 1** Presenting symptoms in the 20 patients with Crohn's disease

Symptoms	Number	Percentage
Diarrhoea	14	70
Abdominal pain	11	55
Fever	12	60
Bloody diarrhoea	2	10
Perianal disease	5	25
Skin lesions (rash)	1	5
Oral ulcers	6	30
Perineal ulcers	1	5

**Table 2** The disease phenotype according to Vienna classification (n=20)

	Number	Percentage
Location		
Ileal (L1)	4	20
Colonic (L2)	7	36
Ileo-colonic (L3)	9	45
Upper gastrointestinal (L4)	5	25
Behaviour		
Non-stricturing non-penetrating (B1)	10	50
Stricturing (B2)	4	20
Penetrating (B3)	6	30

473±134x10<sup>9</sup>/L (normal: 100~300x10<sup>9</sup>/L) and 65% patients had low albumin with a mean±SD albumin level of 24±6 g/L (normal range: 35~55 g/L). C-reactive protein (CRP) of 14 patients were increased to different degrees, moreover.

### **Endoscopic Evaluation**

Among 16 patients undergoing colonoscopy, the complete test failed to be performed with 2 patients due to stricture in colon. In these 2 cases, the colonoscope was only advanced until transverse colon, whereas the colonoscope travelled into ileo-cecal junction in the other 14 cases. Endoscopic findings were as follows: ulcerated lesions, mostly as deep, irregularly shaped and map-like ulcers, in 8 (50%); but aphthous ulcers or cleft-like ulcers only in few cases; intestinal stenosis in 4 (25%); segmental lesions in 6 (37.5%); cobblestone lesions in 3 (18.8%). Other non-specific symptoms like mucosal hyperaemia, edema, erosion, dim vascular texture and purulent secretion could be seen.

### **Treatment and Remission**

Medications used to treat Crohn's disease included Sulfasalazine (4, 20%), 5-aminosalicylic acid (9, 45%), corticosteroid (9, 45%), acetazolamide (1, 5%). Surgery was required in 5 cases. Fistulotomy was performed on 2 patients, because anal fistula recurred; intestinal anastomosis was performed on one patient and enterolysis on 2 patients. Thirteen patients had remission after treatment. However the condition was not improved in 5 cases. Postoperative intestinal fistula caused death in one case and in the other case, death resulted from complication.

## **Discussion**

There are very few reports of prevalence of CD in China over the period 1997 to 2006. One review, which extrapolated the crude prevalence rate based on 55 years of research in China (which included the Chinese literature), calculated the prevalence of CD to be 2.29 per 100 000 person-years.<sup>4</sup> Diversity of paediatric CD's clinical presentation may cause the inaccurate diagnosis. Some reports indicate that incidence of paediatric CD is continuing to rise and is approaching or surpassing that of UC.<sup>5</sup> In this review, we analysed 20 hospitalisation cases of paediatric CD in recent 13 years. Only one case was diagnosed before 2003, while the other 19 cases were identified from 2003 to

2013, which partly indicated an increase in incidence. Paediatrician's awareness of CD and Children's lifestyle changes (development of obesity) may be correlated with this condition.

The highest incidence rates and prevalence of UC and CD have been reported in northern Europe, the United Kingdom and North America, especially in the Caucasian population.<sup>6</sup> All children in our study were Han Chinese ethnicity, mostly lived in Asia. Novel genes identified in Asian CD patients provide an opportunity to explore new disease-associated mechanisms in this population of rising incidence. Nucleotide oligomerisation domain (NOD)-2 variants associated with CD patients in the West have not been identified in CD in the Han Chinese populations.<sup>7</sup> However, Han Chinese with CD are associated with new NOD2 mutations (P268S).<sup>8</sup> In Caucasians, cytotoxic T-lymphocyte antigen-4 variant may be related to CD susceptibility, and Toll-like receptor gene polymorphisms confer a significant risk for developing CD.<sup>9</sup> The autophagy-related protein 16-like 1 (ATG16L1) mutation also demonstrates global variation, with linkage to CD in the West not in China.<sup>10</sup> A single IL-23R nucleotide polymorphism, Gly149Arg, was protective of CD in Han Chinese.<sup>11</sup>

In our study, there was no significant gender difference among the children patients. CD manifested in children aged 10-14 years up to 40%. Although the development of CD in infancy is rare, 3 cases were still found in our study. Published data from CD registries in North America and Europe suggested that less than 1% children with IBD present during the first 12 months of life.<sup>12</sup> However, in our study, distinguished from Pashankar's report,<sup>13</sup> colon was affected in infant patients but no perianal disease was presented.

The most common clinical symptoms are listed as follows: diarrhoea, fever, abdominal pain and blood stool. Abdominal pain presented in some children and is probably caused by tenderness and muscle contraction, which is often misdiagnosed as acute abdomen. In addition, growth retardation is a common and problematic feature of CD and provides important clues to diagnosis. The current treatment regimens focus on inducing and maintaining remission to prevent relapse of disease. Growth impairment, rather than other symptoms, has predominant influence on children through the whole life. All the children in our study presented with growth retardation or malnutrition, but none of them visited doctors seeking diagnosis and treatment of growth impairment.

Some extra intestinal manifestations often occur in IBD

patients, such as skin erythema nodosum, perianal ulcers, arthritis, oral mucosal lesion and conjunctivitis. Autoimmune hepatitis is also reported in some literature.<sup>14</sup> At least one type of extra intestinal manifestation was found in 35% of patients in our study and oral ulcer was most commonly seen. In one female patient, oral and perianal ulcers occurred simultaneously.

The sites of the involvement were ileo-colon (45%) and colon (35%). The cases in which the upper gastrointestinal tract was involved might be probably more than the statistics suggested, because not all the patients underwent the upper gastrointestinal endoscopy. According to Cameron,<sup>15</sup> 26% of CD patients were asymptomatic at presentation. Therefore, upper gastrointestinal endoscopy is incorporated into the routine tests for IBD patients by Yuying Children's Hospital, Wenzhou, China. Most of children with CD develop the inflammatory complication at diagnosis. As was reported, stricturing disease was clearly a complication of small intestinal disease, whereas penetrating disease complicated CD with colonic involvement. It was concluded that disease behaviour was strongly associated with the location of lesions.<sup>16,17</sup> In our study, conversely, there is no finding to confirm the correlation between disease behaviour and location.

The laboratory tests showed that most patients presented with anaemia and thrombocytosis. Cabrera-Abreu et al<sup>18</sup> reported the presence of anaemia or thrombocytosis was associated with diagnostic sensitivity of 90.8%, a specificity of 80%, and positive predictive value of 94.4%. Combined with erythrocyte sedimentation rate, CRP, performance of blood tests was suggestive in diagnosis of CD.

Currently, Crohn's disease can not be cured and the most efficient treatment is to induce and maintain remission, preventing the occurrence of complications. Especially for children with CD, ensuring good nutrition is an important part of management of Crohn's disease and improvement of children's growth and development. The drug treatment for children is based on the extrapolation from the treatment for adults. The guidelines used for adults are recommended to children as well unless otherwise specified. Most of children are firstly treated with drugs containing Mesalamine. Corticosteroids are used when children's CD is flaring. Immunosuppressive drugs may help corticosteroids work better in case of steroids resistance. In general, flare-up episodes are treated with the immunosuppressive drugs in case of mild symptoms (within one year of diagnosis). Lowering or withdrawing the dose

of corticosteroids can benefit children's growth and development.<sup>19</sup> Immunosuppressive therapy may improve the natural history of this disease and decrease the need for performing surgery.<sup>20</sup> Enteral nutrition therapy is considered to be one of the popular therapies in the world, which has been shown to be as efficacious as corticosteroids in inducing remission in children with Crohn's disease with additional nutritional benefits.<sup>21</sup> In long term of use, enteral nutrition is effective in inducing the intestinal mucosal healing and improving the growth and development in children patients. However, it is difficult to popularise enteral nutrition therapy in China, because it is still costly to Chinese patients. The newly introduced infliximab in some literature has modified the treatment of moderate to severe Crohn's disease associated with perianal fistulas.<sup>22</sup> However, the long-term use of infliximab therapy may probably cause some complications like infections and tumour.

Surgery is reserved for the patients after unsuccessful medical therapy. There are two third Children with CD having surgery over their lifetime.<sup>23</sup> The goal of surgery is to resect lesion, moderate poisoning symptom and relieve the bowel obstruction. Surgical treatment is not recommended unless the medical therapy is unsuccessful and complications like haemorrhage, intestinal stricture occur. Following surgical resection of lesions, 5-aminosalicylic or the immunosuppressive drugs are used to reduce the intestinal complications with decreased relapse rate. Crohn's disease can lead to poor prognosis or even higher mobility rate especially in children with early CD, compared to adults or the children with late disease. In our study, two children died of undiagnosed disease in early stage.

## Conclusion

The rising incidence and prevalence of IBD in China is likely related to the changing environment in developing nations such as economic growth, changing diet, drug exposure, changing hygiene and stress levels. Currently, the diagnosis and treatment of children IBD are still problematic in China. Paediatricians should be aware of various presentations of CD since early recognition of the disease and timely medical treatment helps in achieving control of the disease and avoids its complications. A prospective population-based study will be needed to explore the exact incidence and phenotypes of childhood IBD patients in China.

## Conflict of Interest

The authors declared that they have no conflicts of interests.

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