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Retrospective analysis of 515 cases of Crohn’s disease hospitalization in China: Nationwide study from 1990 to 2003

APDW2004 Chinese IBD Working Group

Key words
analysis, China, Crohn’s disease, hospitalized, retrospective.

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Abstract

Background: The purpose of the present paper was to investigate the status of Crohn’s disease hospitalization in China.

Methods: Medical records of hospitalized Crohn’s disease came from 22 medical centers across China during 1990–2003 and were retrospectively reviewed. Every incident case was recorded in detail on a regular comprehensive datum form by investigators in person. Clinical manifestations, examinations and therapeutic status were analyzed.

Results: A total of 515 cases of Crohn’s disease were found. The ratio of patients with Crohn’s disease to total hospitalized patients has increased steadily year by year. Endoscopy was performed in 348 patients (67.57%). Barium meal or enema was performed in 221 patients (42.91%). Histological examination (endoscopical or surgical biopsy) was performed in 340 patients (66.02%). Reasonable treatment strategies were used for 435 patients (84.47%). The evaluation of quality of life for 54/303 patients (17.82%) was poor.

Conclusions: This retrospective, hospital-based study shows that the number of patients with Crohn’s disease in China has steadily increased over a period of 14 years. Further population-based epidemiological studies specifically focusing on risk factors are needed. The diagnosis of Crohn’s disease and therapeutic strategy require improvement.

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Introduction

Crohn’s disease (CD) is a chronic inflammatory bowel disease of unknown etiology, and it is a chronic transmural inflammation that may involve any part of the alimentary tract. The incidence of CD is very low; clinical manifestations are various. It is difficult to obtain definite diagnosis early. In recent years, more and more articles on CD have been published; many previous epidemiological studies found that some Western countries had an increase in the incidence of CD. Furthermore, some gastroenterologists have suspected that the incidence of CD is tending upward. Despite the increasing Chinese articles on CD we cannot find one study of CD on a large scale with many medical centers involved. The epidemiological situation of CD in China remains unknown.

In 2003 some Chinese gastroenterologists attended a meeting in Beijing to investigate the situation of hospitalized CD in China. There were 22 medical centers involved. A standard protocol was adopted for data collection and analysis. We report here the final epidemiological findings, and hope that they will provide more valuable information for proper diagnosis, management and prevention of the disease.

Methods

In order to extract authentic national information of CD, 11 areas were sampled from medical centers all over China. Investigators interested in participating were invited to take part if their center satisfied the following requirements: (i) the medical center was a university hospital or grade A tertiary hospital; (ii) diagnostic facilities for high-quality endoscopy, radiology and pathology were available; and (iii) the center was part of a health-care system that offered universal cover for primary and specialist services with an established system for referral from primary to secondary care.

The medical records of hospitalized CD from 22 hospitals in these 11 areas during 1990–2003 were reviewed. The study areas included Beijing, Tianjing and Shandong Province from northern China; Shanghai and Jiangsu Province from eastern China; Guangdong and Jiangxi Province from southern China; Sichuan and Shanxi Province from western China; and Hunan and Hubei province from central China.

Every case was checked repeatedly, according to the suggested guidelines for diagnosis of inflammatory bowel disease. After excluding chronic intestinal infections (intestinal tuberculosis, amebiasis and Yersinia), intestinal lymphoma, diverticulitis, ischemic colitis, and Bechet’s disease, the diagnostic procedure was as follows (numbered items are as given in Table 1): (i) patients with items 1, 2 and 3 are presumptively diagnosed, but can be definitively diagnosed when one of items 4, 5 or 6 is also present; patients with item 4 and two of items 1, 2, or 3 can also be definitively diagnosed; (ii) typical clinical presentation with positive radiological, endoscopic and biopsy features can confirm the
diagnosis; (iii) typical clinical presentation with positive radiological or endoscopic findings can be used to make a presumptive diagnosis; (iv) when clinical presentation suggests CD, further examinations should be carried out; (v) patients with a first attack but without characteristic clinical, radiological, endoscopic or biopsy findings should be followed up for 3–6 months; if it is difficult to differentiate the condition from intestinal tuberculosis, the patient should be treated as having tuberculosis and the therapeutic effect observed.

The diagnosis of CD had been on the basis of endoscopic, radiological or pathological evidence, besides clinical manifestation according to medical records. Those patients verified were included in the study. If a patient with CD had been in hospital several times, only the first medical record was reviewed. The date of diagnosis (taken as the date the patient was admitted) was used for the analysis of ratio of CD to total hospitalized patients.

To achieve a complete record of incident cases as well as consistency of methods among various centers, a comprehensive data form for CD was established. Every incident case was recorded in detail on the form by investigators in person. Patient data were collected on age, gender, occupation, main clinical manifestations and their duration, endoscopic and radiologic investigations, biopsies taken and histological abnormalities, type of diagnosis, medical treatment and their outcomes, and any surgery performed.

Results

A total of 515 cases were included from 22 hospitals in 11 areas in China from 1990 to 2003. There were 322 male patients and 193 female patients; the CD ratio of male to female was 1.67:1. Patient age ranged from 2 to 77 years old, the mean age at diagnosis was 37.7 ± 20.5 years (mean ± SD). The course of CD was from 3 days to 32 years. Table 2 shows the age-specific cases (per decade) for CD. Peak prevalence of CD occurred among the age groups of 20–50 years. Table 3 shows that the year-specific ratio of CD to all hospitalized patients steadily increased year by year during the period from 1990 to 2003. The ratio (22.28843 × 10⁻⁵) in 2003 was 2.78-fold higher than that (8.014133 × 10⁻⁵) in 1990.

Clinical manifestations

In the present study there was a large degree of variation in the clinical manifestations of CD. The most common manifestation was abdominal pain in 429 cases (83.3%), followed by diarrhea, loss of weight, fever and so on. In complications, the most common was hemorrhage in 134 cases (26.02%), followed by intestinal obstruction in 92 cases (17.86%). The well-known manifestations such as fistula, abdominal mass and perforation were less common, and extraintestinal manifestations uncommon (Table 4).

Accessory examinations

Accessory examinations consisted of endoscopy, barium and histology; 120 of the 515 patients had all three. A total of 348 patients (67.57%) underwent endoscopy. The most common findings of endoscopy were segmental lesion and ulcer; by contrast, the least were cobblestone and shortened intestinal tract.

Barium meal or enema was performed in 221 patients (42.91%). String sign was found in 93 patients (42.08%), but jumping sign, fistula, cobblestone were uncommon.

Histological examination (endoscopical or surgical biopsy) was performed in 340 cases (66.02%). More valuable features were

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<th>Table 1</th>
<th>World Health Organization diagnostic criteria for Crohn’s disease</th>
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<tr>
<td>Item</td>
<td>Clinical</td>
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<tr>
<td>1. Discontinuous or segmental lesions</td>
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<td>2. Cobblestone appearance or longitudinal ulcer</td>
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<td>3. Transmural inflammation</td>
<td>+ (Abdominal)</td>
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<td>4. Non-caseating granulomas</td>
<td>+</td>
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<td>5. Fissures and fistula</td>
<td>+</td>
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<td>6. Perianal disorders</td>
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<th>Table 2</th>
<th>Age distribution of Crohn’s disease</th>
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<td>Age group (years)</td>
<td>Patients (n)</td>
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<tr>
<td>1–10</td>
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<td>11–20</td>
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<th>Table 3</th>
<th>Hospitalized CD for 22 medical centers in China 1990–2003</th>
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<tr>
<td>Years</td>
<td>Patients (n)</td>
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<td>1990</td>
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<td>2002</td>
<td>71</td>
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<td>2003</td>
<td>83</td>
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CD, Crohn’s disease.
found only in a small number of these patients. For example, non-caseous granuloma was discovered in 105 cases (30.88%), fissuring ulcer in 63 cases (18.53%), transmural inflammation in 44 cases (12.94%) and skip lesion in 14 cases (4.12%; Table 5).

### Type, degree and stage of disease

Table 6 indicates that in the present study, 146 patients (38.35%) had isolated small bowel disease and 187 patients (36.31%) had colonic disease, while 162 patients (17.86%) had both small bowel and colonic involvement, and 20/515 patients (3.88%) had both colon and anus involvement. As for behavior categories of these CD cases, there were 185 cases of diarrhea type (35.92%), 100 cases of hemorrhage type (19.42%), 92 cases of obstruction type (17.86%), 63 cases of appendicitis type (12.33%), 45 cases of abdominal mass type (8.74%), and 30 cases of fistula type (8.52%). According to CD activity index (CDAI) by Harvey and Bradshaw, 5 83 patients (16.11%) had mild CD, 260 patients (50.49%) had moderate CD and 172 patients (33.40%) had severe CD. At diagnosis, 457 patients (88.74%) had active CD while 58 patients (11.28%) were in remission.

### Diagnosis

The number of patients who underwent endoscopy, radiology and histology (endoscopical or surgical biopsy) were 348, 221 and 340, respectively. Any single item of examination would not give a high rate of correct diagnosis, which was similar to the rate of doubtful CD (Table 7). Combined with the clinical manifestations and the diagnosis of endoscopy, radiology and histology, review of the case data suggested that 205 CD patients (39.80%) were diagnosed definitely at admission, 18 patients (3.50%) had suspected CD and 292 patients (56.70%) were misdiagnosed. A total of 120 of the 515 patients underwent all three kinds of accessory examinations, and every patient had at least one kind of accessory examination. Only 348 patients (67.5%) underwent an endoscopic examination, and histological information was available in only 340 patients (66.2%). However, the 340 histological examinations included not only endoscopical biopsy but resected...
specimen as well. According to Chinese guidelines, a typical clinical presentation with positive radiological or endoscopic findings can be used to make a presumptive diagnosis. For example, some of the 384 patients had only a presumptive diagnosis without biopsy. After admission, 60 patients obtained a presumptive diagnosis of CD by means of surgery without pathological examination, 100 patients obtained it only by means of barium meal or enema. Although some diagnoses had been presumptive primarily, every patient was later given an effective anti-CD treatment. These diagnoses were confirmed by means of diagnostic treatment.

In the misdiagnosed patients, 40 were diagnosed as having cancer, 30 were diagnosed as having intestinal tuberculosis, 27 as having peri-appendicular abscess or appendicitis, 20 as having ulcerative colitis, 16 as having infective colitis, 15 as having intestinal lymphoma, 13 as having chronic colitis, 10 as having peptic ulcer, four as having acute pancreatitis, three as having anaphylactic purpura, two as having Behçet’s disease, and two as having eosinophilic colitis. In the present investigation, antituberculosis treatment was given to six patients who were diagnosed as having intestinal tuberculosis at presentation before a final diagnosis of CD was made. It was so difficult to diagnose that as many as 110 patients who were not suspected to have CD at admission. These patients were given a diagnosis due to abdominal pain, diarrhea, hemorrhage or fever. After having undergone some examinations, most patients had a presumptive or definite diagnosis. As for surgery, 171 patients had undergone surgical intervention, 79 patients finally obtained correct diagnosis after operation, in which 31 patients obtained a definite diagnosis by means of laparotomy exploration, and 48 patients underwent re-diagnosis after operation.

### Treatment

Medications and therapeutic approaches were not perfectly decided with reference to the course of the disease and previous therapies. To control the attack, 435 CD patients (84.47%) had adopted one regular treatment strategy consisting of salazosulfapyridine (SASP)/5-aminosalicylic acid (5-ASA) (A), glucocorticoid (B), surgical intervention (C) and/or immunosuppressant (D). The most common strategy was only A in 151 cases, followed by only C in 101 cases, and 163 out of 435 cases (37.47%) were treated with a combined strategy. The others had taken traditional herb, anti-diarrheal, antispasm and so on. The treatment strategies are listed in Table 8.

Table 9 shows that glucocorticoids were given to 148 cases (28.74%). A total of 121 patients had taken glucocorticoids orally. Intravenous steroids were given to 58 patients. Topical steroids were given to 22 patients. A total of 297 patients (57.67%) had SASP (n = 166) or 5-ASA (n = 131). Immunosupressants were given to 24 patients (4.66%): azathioprine, n = 18; 6-mercaptopurine (6-MP), n = 2; and cyclosporine, n = 3. Antibiotics were found in 235 patients (45.63%), in which ciprofloxacin or norfloxacin was identified in 47 patients and metronidazole in 128 patients. Sixty-two patients had taken traditional herb.
Quality of life

Two hundred and fourteen patients (41.55%) achieved complete remission. The treatment was effective in 268 cases (52.04%), but 26 patients (5.05%) did not respond to the strategy; and seven patients (1.36%) died. A total of 303 patients (58.83%) had undergone an evaluation of quality of life: good in 33/303 cases (10.89%), normal in 216/303 cases (71.23%), and bad in 54/303 cases (17.82%).

Discussion

This is the first large-scale multicenter study of CD incidence in China. The study was a retrospective analysis of hospitalized patients. The number of newly diagnosed CD cases has been growing steadily; furthermore, the ratio of hospitalized CD to all diseases in 2003 was 2.78-fold higher than that in 1990. Accurate incidence could not be determined without an analysis on the basis of the population in the areas involved, but it appears that CD incidence is on the increase in China. Jiang and Cui reported that the number of new cases of CD in the last 10 years was threefold more than that in the previous 10 years. In Japan and Korea there has also been an increase in the incidence of CD during the period of rapidly developing economy. Similar findings have been found in African-Americans in recent years. It is possible that the phenomenon is due partly to the improvement of the health system and knowledge of disease and diagnostic technology, but Westernized lifestyle, citified countries and industrialization also contribute to development of CD.

Our findings agree with that of Japanese researchers, who found that the incidence of CD had a male preponderance. The role of smoking in inflammatory bowel disease remains of interest because, unlike UC, smoking not only predisposes to CD, but also adversely affects the course of the disease. In the present study the proportion of smokers in men was much higher than that in women, which might account for the phenomenon. In contrast, there was no such difference, or it had a female preponderance in Western countries. There should be unknown factors besides smoking.

In the present study CD was primarily a disease of adulthood, with the peak incidence occurring between 30 and 40 years of age. Approximately 26.41% of the patients were diagnosed during the third decade of life. However, Russel and Stockbrugger reported that in Western countries CD was primarily a disease of adolescence and young adulthood, and that the peak incidence occurred during the period from 15 to 30 years of age. In the present study, however, patients were generally older than those reported by Russel and Stockbrugger; there were only 11 patients with CD who were under 10 years old. This might be because CD was not highlighted. It is a pity that our study excluded pediatric hospitals because some young patients with CD were treated not in the department of pediatrics in the medical center but in pediatric hospitals, and therefore they were omitted from the present study.

Clinical manifestation

Our study agreed with that of Kornbluth et al. in that the main manifestations of CD were abdominal pain, diarrhea, weight loss and so on. Classic specific manifestations such as non-caseous granuloma, skip lesion and cobblestone were uncommon.

However, our investigation found that there were fewer small bowel diseases than colonic diseases in Chinese patients. Although both Paul et al. and Mekhjian et al. found that 30–50% CD not only involved the small bowel but also involved the colon, which was consistent with our study, they reported that small bowel diseases were more common than colonic diseases.

The aforementioned difference of location of CD between Chinese patients and Western patients might reflect the actual state, but the difference may be explained by other possible causes: first, colonoscopy or barium enema was more accessible to patients in Chinese medical centers than in Western countries; second, capsule endoscopy or small intestinal endoscopy was less accessible to patients in Chinese medical centers than in Western countries; and third, the rate of surgical intervention was lower in China than in Western countries. In order to improve the positive finding ratio of lesion in small bowel, doctors may turn to trans-abdominal bowel sonography (BS) and Tc-99 m-HMPAO leukocyte scintigraphy (LS).

Goldman et al. noted that extraintestinal manifestations were present in all 15 patients, and perineal disease was present in more than half of their patients. Fistulizing disease other than perianal disease was present in 3/15 patients (20%). In contrast to the present study, only 115 cases had extraintestinal manifestations. Unfortunately, there are no reports relating to the anus in the present study, the phenomenon may reflect the fact that doctor and patient in China are not comfortable talking about this.

Diagnosis

The percentage of CD patients who underwent endoscopy, radiology (barium enema or meal), or histology (endoscopic or surgical biopsy), ranged from 40% to 60%. A single item of investigation could only give a moderate rate of definite diagnosis of CD; most of the patients were given a diagnosis of suspected CD or were misdiagnosed. The correct diagnosis should be based on analysis of the comprehensive accessory investigations, as well as history and physical examinations. There was no so-called characteristic dominant finding. Doctors often could not make a correct diagnosis at first. Owing to lack of sufficient knowledge of CD, they would give a non-significant diagnosis such as ‘abdominal, hemorrhage or fever’. Tuberculosis is a very important infective disease in China, and the digestive tract is often involved. Therefore, among the misdiagnoses, intestinal tuberculosis was quite common. According to Gan et al., biopsy is of limited diagnostic value in the differentiation of intestinal tuberculosis from CD, and polymerase chain reaction is valuable in the differentiation between intestinal tuberculosis and CD.

Treatment

Loftus et al. reported that less than half of the patients require corticosteroids at any point. During any given year, approximately 10% of patients are treated with corticosteroids and 30%
are treated with 5-aminosalicylates. Up to 57% of the patients require at least one surgical resection. Between 400,000 and 600,000 patients in North America have CD, and the natural history is marked by frequent exacerbations requiring treatment with corticosteroids, 5-aminosalicylate products and surgery.

From the present study we can draw two conclusions. First, all of the therapeutic strategies were not based upon the disease location, severity and complications. For example, the rate of patients treated with corticosteroids was higher than that of Lofthus et al.21 Initially some mild active diseases were not treated with an oral aminosalicylate but with corticosteroids. Immunosuppressants were not used widely in China. Second, the choice of drug was limited. Infusions of infliximab are an effective adjunct and may be an alternative to steroid therapy in selected patients in whom corticosteroids are contraindicated or ineffective.22 There were no patients who had ever taken it in the present study; nor had any of them taken tacrolimus. These two kinds of drugs could not be obtained by doctors in China, especially infliximab. This fact might account for the lack of immunosuppressants in CD. In contrast, because China is a developing country, the two drugs are too expensive to prescribe for patients. In view of costs, azathioprine and 6-MP should be adopted in severe CD, to maintain remission. Budesonide may become an available alternative in the near future.

Therapeutic recommendations should depend upon the disease location, severity, and complications. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention; therapy is sequential to treat acute disease then to maintain remission. Surgery is advocated for obstructing stenoses, supplicative complications, or medically intractable disease.23

Quality of life

The Straus et al. study also utilized a quality of life questionnaire that found that African-Americans had lower quality of life, had more days of work lost, or loss of work entirely due to their disease.24 In the present study, the results were similar to that study in terms of access to care, they were less likely to have health insurance, and reported greater difficulty seeing a doctor for financial reasons. These psychological and socioeconomic factors may impact on a number of factors including frequency of clinical visits and compliance with medical management, all of which are likely to have a profound impact on disease course.

Neither incidence nor prevalence of CD has ever been reported in China. However, through our retrospective nationwide large-scale multicenter survey covering the last 14 years, a steady increase year by year in the number of CD patients has been observed. The status of clinical features, diagnosis and treatment of CD in China was different from that in Western countries, which may be associated with psychological, socioeconomic factors and health insurance, as well as racial and geographic variations. To date, most studies of CD have been performed in the developed Western countries. Accurate data are lacking in developing countries, especially in China. Therefore, it is necessary to organize a population-based epidemiological investigation of CD in the near future, so as to improve the level of prevention and patient care.

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