Long-term clinical behaviour of jejunoileal involvement in Crohn's disease

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Diffuse and extensive jejunoileal Crohn's disease is an uncommon entity. In 39 patients, including 21 males and 18 females, followed for a mean duration of over 16 years between 1979 and 2004, the extent of disease was defined and disease behaviour characterized. Over 80% of patients had concomitant colonic and/or gastroduodenal involvement with Crohn's disease, suggesting that this entity may represent a specific clinical phenotype of extensive disease localization. Classification of Crohn's disease behaviour using the Vienna classification schema revealed that virtually all patients in this study suffered from intestinal stricture formation or penetrating disease complications. Moreover, pharmacological therapies with corticosteroids and immunosuppressant drugs were rarely successful, with virtually all patients requiring at least one, and usually multiple, intestinal resections. Finally, most patients required long-term nutritional support, often with home parenteral nutrition. New treatments are required, possibly defined on the basis of their effectiveness in reducing the severity and extent of intestinal disease, rather than more conventional statistically driven reductions in disease activity indexes.

Key Words: *Crohn's disease; Jejunoileitis; Nutritional support; Small bowel disease; Vienna classification*

Crohn's disease is a heterogeneous inflammatory disorder that may involve any site in the gastrointestinal tract. The inflammatory process is typically characterized as being discontinuous, patchy or focal in nature, and usually involves the ileum and/or colon. Upper gastrointestinal tract involvement also occurs, particularly in the stomach and duodenum. Diffuse jejunoileal involvement represents another pattern, with or without involvement of the more proximal or distal intestinal tract (1,2). Recent efforts (3) have resulted in development of a classification system to permit analysis of more homogeneous Crohn's disease patient groups based on age at diagnosis, site of involvement and disease behaviour (3). In this schema, disease has been categorized as localized to the upper gastrointestinal tract even though there may be concomitant involvement of other sites (eg, ileum or colon).

For the present study, 39 consecutive patients with diffuse jejunoileal involvement from a larger Crohn's disease group of 1015 patients seen over more than two decades were evaluated.

Le comportement clinique à long terme de l'atteinte jéjuno-iléale de la maladie de Crohn

La maladie de Crohn jéjuno-iléale diffuse et étendue est une occurrence rare. Chez 39 patients, soit 21 hommes et 18 femmes, suivis pendant une durée moyenne de 16 ans entre 1979 et 2004, l'étendue de la maladie a été définie et le comportement de la maladie, caractérisé. Plus de 80 % des patients présentaient une atteinte colique ou gastroduodénale concomitante à la maladie de Crohn, laissant supposer que cette maladie peut constituer le phénotype clinique précis d'un foyer étendu de la maladie. La classification du comportement de la maladie de Crohn au moyen du schéma de classification de Vienne révèle que pratiquement tous les patients de l'étude souffraient d'un rétrécissement intestinal ou de complications d'une maladie pénétrante. De plus, la pharmacologie aux corticoïdes et aux immunosuppresseurs était rarement efficace, pratiquement tous les patients ayant besoin d'au moins une résection intestinale et généralement de multiples résections. Enfin, la plupart des patients avaient besoin d'un soutien nutritionnel à long terme, souvent accompagné d'un type d'alimentation parentérale. De nouveaux traitements s'imposent, peut-être définis par leur efficacité à réduire la gravité et l'étendue de la maladie intestinale plutôt que par des réductions statistiques classiques des indices d'activité de la maladie.

The results in the present paper show that the clinical course of Crohn's disease in a subset of patients with diffuse and extensive jejunoileal disease is extremely difficult, necessitating repeated intestinal resections and a frequent requirement for long-term nutritional support.

PATIENTS AND METHODS

Definitions and inclusions

The patients in the present study were derived from a clinical database with 1015 consecutively evaluated Crohn's disease patients, directly treated by the investigator over more than two decades (4-6). Although the mean follow-up period for this entire patient group was over 10 years (4), the mean follow-up period for the jejunoileal group was 16.8 years, similar to a prior report describing a single-centre experience with this disease (2).

In earlier studies (4-6), the overall patient database was found to be female-predominant with over 80% diagnosed before 40 years of age. In addition, the disease was classified as being localized to ileum and/or colon in over 80% of patients. Finally, more than

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Figure 1) Age at diagnosis of Crohn's disease for 39 male and female patients with diffuse and extensive jejunoileal disease expressed in percentages for each age group

70% had complex disease with either strictures or penetrating complications. As described previously (4), for all patients in this evaluation, office and inpatient hospitalization records as well as endoscopic, radiological imaging, surgical and pathology reports were recorded. Statistical analyses were performed using Student's *t* test or χ^2 analysis.

Jejunioleal involvement

Patients with jejunoileal involvement were usually diagnosed on the basis of typical radiological features, but in virtually all patients, the diagnosis was eventually confirmed both with laparotomy and histologically in resected small intestine (2). In one male patient, followed by the investigator for over 24 years, and in one female patient, followed for over 18 years, intestinal resections have not been required to date. In these two patients, histological confirmation of granulomatous disease was initially documented in multiple small intestinal sites using a gas-activated hydraulic multisite small intestinal biopsy instrument (Quinton Instruments, USA) (7) or with an Olympus SIF small intestinal fiberscope type B (Olympus, Japan) (8). In addition, all of these patients have undergone upper endoscopic and colonoscopic studies with multiple site biopsies.

CLASSIFICATION METHOD

Male and female patients were each classified based on a prior published schema developed elsewhere (3) and applied previously by this investigator to a single clinician Crohn's disease database (4). For the present purposes, however, modification of this Vienna schema was necessary for age at diagnosis because this classification schema does not specify a category of specific age groups under the age of 20 years. Information for the present study, therefore, included the age at diagnosis before the age of 20 years based on a previous modification (6). Other defining features of the Vienna classification were used including: location of disease defined as the maximal extent of disease, or disease at the first resection (ie, L1, ileum, possibly involving cecum; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract regardless of other disease sites) and disease behaviour (eg, B1, nonstricturing and nonpenetrating; B2, stricturing; B3, penetrating). In this classification schema, disease is defined as B3 if, at any time during the course of

Figure 2) Other sites of Crohn's disease involvement in male and female patients with jejunoileal disease expressed as the percentage of patients with disease localization at a specific site

the disease, intra-abdominal or perianal fistula, perianal ulceration, inflammatory mass and/or abscess have developed, even if a coexisting stricture is present. In contrast to the definition of disease location, definition of disease behaviour in the Vienna classification has no specific time limit. For the present study, disease behaviour was defined in a cumulative fashion at the most recent patient encounter during the previous three years.

RESULTS

Sex and age distribution

There were 449 males (44.2%) and 566 females (55.8%) with Crohn's disease consecutively evaluated over two decades in this single clinician database. To date, only two patients (both female) with jejunoileal involvement have died, one from superimposed cerebral involvement with systemic lupus erythematosus and one from a dilated cardiomyopathy complicated by congestive heart failure. Figure 1 shows the distribution of males and females with diffuse jejunoileal involvement in each age group. There were 39 patients, representing 3.8% of the entire patient database. As shown, there were 21 males (53.8%) and 19 females (48.7%) with diffuse and extensive jejunoileal involvement, and this represented 4.7% of all males and 3.4% of all females. These results approximate the estimated percentage of 5.7% from a similar large single-centre series of 653 patients with diffuse jejunoileitis in Crohn's disease that included fewer patients (14 males and 20 females) (2). Figure 1 also shows that over 90% of the patients in the present study were diagnosed before the age of 40 years compared with 10% over age 40 years ($P < 0.05$). This included all of the males and almost 90% of the females. Only two of the females were initially diagnosed with Crohn's disease after the age of 40 years. Mean age at diagnosis was 22.9 years.

Other locations of involvement with jejunoileal disease

With the Vienna classification, all of the patients with diffuse jejunoileal disease were initially classified with upper gastrointestinal tract involvement. Figure 2 schematically illustrates the other sites of involvement detected in these 39 patients with extensive small intestinal disease. As shown, over 80% of patients also had disease in the colon. In addition, duodenal or

Figure 3) Disease behaviour in 39 patients with diffuse and extensive jejunoileal Crohn's disease expressed in percentages for possible types of disease behaviour. NSNP Nonstricturing and nonpenetrating; Penet Penetrating; Strict Stricture

gastric involvement, or both, was also detected in eight males (38.1%) and four females (21.1%). Indeed, among all 39 patients with jejunoileal disease involvement, only a minority, about 10%, had disease localized to the jejunoileum only, while the majority, or about 90%, had more extensive disease involvement ($P < 0.05$).

Disease behaviour

Figure 3 shows disease behaviour for males and females with Crohn's disease classified with jejunoileal involvement. Over 95% had complex disease, with strictures in 16 patients (41.0%) or penetrating disease complications in 22 patients (56.4%). Similar percentages of males and females were affected. These percentages also both exceed the percentages that were previously recorded for males and females for complex disease in the overall database of 1015 Crohn's disease patients (714 patients, 70.3%) as well as for male and female patients classified with strictures (322 patients, 31.7%) or penetrating disease complications (38.6%).

Treatment

Figure 4 shows the treatments during the disease course in these 39 patients. Over 90% had been treated in a 'step-up' fashion with each of 5-aminosalicylates, antibiotics (including metronidazole and ciprofloxacin) and, finally, corticosteroids. Immunosuppressants (ie, imuran, 6-mercaptopurine) were used in 26 patients in doses ranging from 50 mg to 150 mg daily, usually for extended periods of up to four years. To date, only one patient was also treated with infliximab. As might be anticipated in a cohort with complex clinical disease, almost every patient treated with these medications required an intestinal resection, and for approximately 80%, multiple intestinal resections were eventually required during the course of their Crohn's disease. In some, resections were avoided or limited because of the performance of single or multiple stricturoplasties. Also, a significant percentage of males and females required a colectomy during their clinical course, possibly emphasizing the extent and severity of the inflammatory process in this particular patient subgroup with Crohn's disease. Treatment with either corticosteroids

Figure 4) Medical (med) and surgical management of diffuse and extensive jejunoileal Crohn's disease expressed as percentages of patients undergoing each type of treatment. HTPN Home total parenteral nutrition; Res Resection

or immunosuppressants, aimed at reducing the inflammatory process and reducing disease activity, produced a sustained symptomatic improvement in only a single male and a single female patient. Over 50% of males and females required ongoing nutritional support, usually with part- or full-time home parenteral nutrition.

DISCUSSION

The present study evaluated a clinical experience with Crohn's disease in 39 patients with diffuse jejunal and ileal involvement. The results confirm a specific phenotype of Crohn's disease with clinically extensive disease that is fortunately uncommon, but has a high degree of morbidity. This represents an ongoing long-term management challenge because virtually all patients were diagnosed before 40 years of age.

The results here also show further that this disease, while extensively involving the small intestine, is also commonly associated with disease elsewhere in the intestinal tract, particularly in the colon in over 80% of patients. These results are consistent with a prior report (2) of jejunoileal Crohn's disease documenting the results in Birmingham patients evaluated between 1960 and 1991. In that study, the colon was the most commonly involved other disease site, estimated to affect 12 of 34 patients (35.2%), using largely historical imaging modalities (2). That the results of the present study demonstrate even more frequent colonic involvement likely reflects, in part, improved detection with modern colonoscopic visualization compared with the historical reliance on barium radiographic methods. Most important, these findings show that there may be a particular disease phenotype with very extensive involvement of both the small and large intestine. Similar conclusions were derived from a European report (9) of 48 patients with diffuse jejunoileal disease, suggesting that this may be a relatively homogeneous group, a separate and distinct form of Crohn's disease.

The present study also showed that disease behaviour is complex and severe, often with the eventual formation of recurrent strictures and penetrating disease complications. In part, the observations may only reflect the long duration of follow-up of these patients with jejunoileal disease by a single clinician.

Although the Vienna classification was not designed to quantify disease severity or its morbidity, the results, by employing the Vienna schema, underline a particular Crohn's disease phenotype that is associated with a complex clinical disease course. This is reflected by a need for surgical intervention, often intestinal resections with or without stricturoplasties. Usually, extensive and multiple procedures were required, leading to a requirement, in most, for long-term nutritional support. These results also confirm a Baltimore report (10) of 23 children with jejunoileitis requiring aggressive nutritional and surgical intervention.

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