Crohn's disease phenotype, prognosis, and long-term complications : what to expect ?

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Abstract

According to Montreal classification, different phenotypes of Crohn's disease are defined taking into account age at diagnosis, localization of digestive lesions at first surgery, and cumulative anatomical behaviour. This classification is supported by the increased severity of the disease when diagnosed in childhood, the relative stability of disease localization over time, and the clinical importance of intestinal complications as stricture and abscess or fistula formation. However, type and delay of complications are dependent on disease localization (they develop early in small bowel disease and late in colitis), every patient will develop complications one day, and perianal disease may be an important problem observed in up to half the patients. The percentage of patients with active disease every year remains stable, about 40%, after the 3 first years, and only a few patients have long periods of remission. Intestinal resections are required in the majority of patients during life, and many are operated on several times. Prognosis is hampered by iterative surgery, cancer and side-effects of treatment. Standardized mortality ratio is 1.50. Although occurrence of complications, need for surgery and mortality did not change significantly through the years 1950-2000, there are some signals suggesting that new therapetic strategies (immunosuppressants earlier in high risk patients) and biologics will modify natural history and improve the long term prognosis. (Acta gastroenterol. belg., **2008**, 71, **303-307**).

Crohn's disease (CD) is a chronic disabling long-life illness, disconcerting in its evolution, which may be deranged by severe flares and anatomical complications requiring surgery. As CD is diagnosed usually in very young people, a common concern is what will be the long term impact of the disease upon the life project of the patient. Although some prognostic factors have been identified, in particular age at onset and disease localization, evolution remains poorly predictable in one individual. Moreover, until the very last years there was no clear indication that treatment was able to modify the long term natural history of the disease. It is important to make a state of the art of CD phenotype and prognosis at the present time while new biological therapies and changing therapeutic strategies are arriving (1).

CD phenotypes

There have been several attempts to use demographic, clinical and anatomical characteristics to identify subgroups of CD patients who differ in their natural history and complications, defining different phenotypes. The Vienna classification of CD, proposed in 1998 (2), considers three items : age at diagnosis, localization of digestive lesions at first surgery, and cumulative anatomical behaviour, resulting in 24 possible subgroups. This classification was slightly revised in 2005 in Montreal (3) by introducing a new age category, allowing for a simpler localization, and including a modifier for perianal disease.

Age at diagnosis

CD may develop at any age, from less than 2 years to more than 90 years. The Montreal classification recognizes three age categories at diagnosis, 16 years or younger, 17 to 40 years, and older than 40 years. Indeed, the phenotype of disease at diagnosis varies according to the age of onset (4). For example, jejunal and ileal lesions are more common in patients diagnosed with CD in infancy, whereas colonic disease is more prevalent in older patients. Moreover, when comparing cases of similar location and calendar year of diagnosis, we showed that CD with pediatric onset was more severe than CD diagnosed in adulthood, with an increased annual activity rate and a higher requirement of immunosuppressants and biological therapy. Complications and surgery occurred at an age 15-20 years earlier than in adult-onset CD, thus these patients are exposed early in their life to major sequelae (5).

Disease location

CD may involve any part of the gastrointestinal tract, from mouth to anus. However ileal and colonic localization are the more prevalent. The Montreal classification distinguishes disease limited to the terminal ileum with or without spill over into cecum (L1), colitis (L2), and ileocolitis (L3). Any disease location proximal to the terminal ileum, i.e. above the last meter of small bowel above the ileocecal valve, defined in the Vienna classification a fourth location type (L4), which is no longer recognized as a special location. In most large series from the literature, the distribution of patients is approximately one third of L1, one third of L2, and one third of

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L3 (2). Of note, although the extent of involvement present at time of diagnosis may progress, or regress, during follow-up, initial localization determines usually cumulative localization (6). Indeed, in ileal disease, the risk of subsequent colonic lesions is low : less than 20% of patients develop colonic lesions after 10 years of follow-up (7). And a similar minor proportion of patients with colitis only, extend their disease to the small bowel (8).

Perianal location is another important problem in CD (9). At presentation, about 30% of patients share perianal lesions and 20% have or have had a fistula (10). During disease course, the cumulative risk of developing a perianal fistula increases to 45% at 20 yr in the Olmsted County CD population (10), and we observed a very similar cumulative rate in our series of St-Antoine hospital (43.8 ± 1.2% at 20 yr). It should be noted however that this risk of perianal fistula is twice more important in patients with colonic disease (L2 location) than in patients with ileal disease (L1 location) (11), the 20-yr cumulative risks being respectively in our series 57.8 ± 2.3% in L2 and 27.8 ± 1.9% in L1.

Behavior : stricturing, penetrating and inflammatory phenotypes

Greenstein *et al.* (12) in 1988 suggested that patients operated on for a penetrating complication (abscess, fistula, or peritonitis) had an increased risk to develop a surgical recurrence from a similar penetrating complication. Conversely, patients with a stricture tended to recur later and again in a stricturing mode. This distinction led to the definition of three different behaviors : penetrating, stricturing, and non-penetrating non-stricturing (or inflammatory). A hierarchy was introduced, a penetrating disease being considered as more severe than a stricturing disease : the occurrence of any penetrating complication in a patient with a stricture changes the behavior from stricturing to penetrating, whereas the late development of a stricture in a previously penetrating disease does not change the classification. Actually we have shown with Louis *et al.* that the behavioral phenotype is not fixed in one individual but changes with longer follow-up (6,13). During the first years, inflammatory forms predominate largely, whereas complications develop subsequently, and after 30 years most patients had a complication and are classified as having a penetrating, or less often, a stricturing, disease. In other terms, the occurrence of complications is nearly constant in such a life-long disease. In addition, behavior is highly related to disease location. Small bowel involvement may be complicated at diagnosis or during the very first years by an abscess/fistula or by a stricture followed by a fistula formation (14), whereas a colonic disease may remain «uncomplicated», inflammatory, for many years (Fig. 1). It is not unusual to observe the coexistence in the same individual, or even within the same intestinal segment, of both stricturing and penetrating lesions. Perianal disease should be considered in particular because of the anatomy of the anal verge and the potential of these lesions to create fistulae and abscesses (11). The Montreal classification proposed to analyse these lesions separately from the intestinal disease, even though they are more frequently associated with colitis than with small bowel disease (15,16).

Prognosis

Burning out

A question often asked by patients is whether and when they will be cured of the disease, or at least maintaining a long standing remission. In the Copenhagen cohort, cohort which is very valuable because population-based and with a very low rate of lost to follow-up,

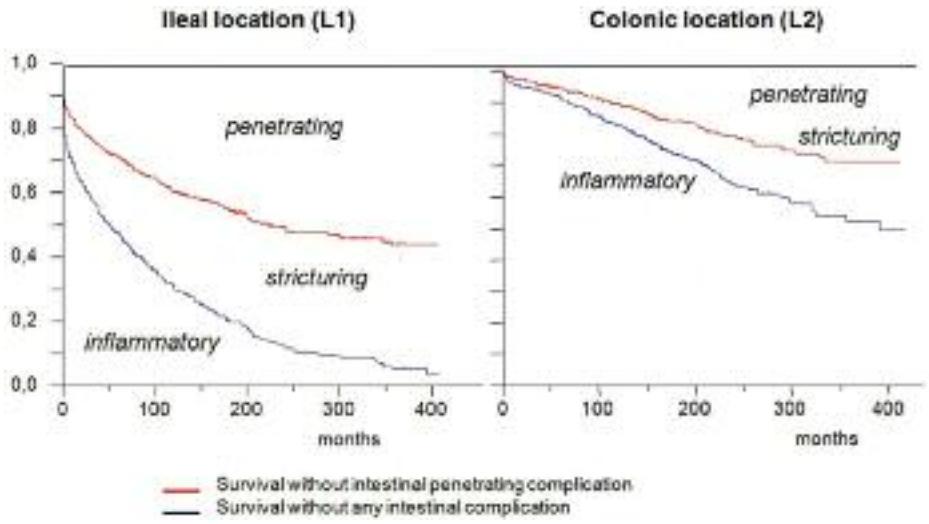

Fig. 1. — Cumulative risk of remaining free of intestinal penetrating complication, and of remaining free of any intestinal complication, respectively, in patients with ileal location (L1, n = 1448) and in patients with colonic location (L2, n = 1129).

there was no clear indication of a decreased activity of the disease. The percentage of patients with active disease remained stable over time, about 45%, after the three first years following diagnosis (17). In the more recent study from Norway, the IBSEN study, although 50% of patients considered that their disease improved during the first five years from diagnosis, there was no clear burning out during the subsequent five years (18). In a prospective study of our cohort, we showed that only a minority of patients, less than 4%, did maintain a prolonged remission from 1995 to 2007 (unpublished data).

Intestinal resection

Progression of the anatomical damage leads to development of complications inaccessible to medical therapy and requiring surgery. Less commonly, medicines fail to control disease activity and removal of the diseased segment is the only alternative. In the Copenhagen cohort, the 20-yr cumulative risk of intestinal resection was 82% (17). Other series from 1970 to 2000 showed rather similar rates (19-21). In our series from St-Antoine hospital (3748 patients in 2007), the 20-yr cumulative risk was 76 ± 2%.

Permanent stoma

Another fear of CD patients is the risk of permanent stoma. Proctocolectomy for Crohn's colitis is less often performed, as segmental colonic resection gives somewhat similar results to total colectomy (22). However permanent fecal diversion may still be necessary in patients with disabling chronic active perianal disease non responding to immunosuppressants and biologics. Among patients with perianal disease, it was estimated that roughly half of patients required permanent fecal diversion, which was even more frequently true for patients with colonic CD and anal stenosis. That means 12% of the total CD population in that recent surgical series from the US (23). In our series the cumulative risk of permanent stoma was 13 ± 1% twenty years after disease onset. Although infliximab may be efficient in most patients with perianal disease in the mid term (24), its impact on the need for permanent stoma remains to be evaluated.

Effect of treatment on natural history

There are no data demonstrating a clear improvement through the period 1950-2000 in disease activity, occurrence of complications and need for surgery. For example, curves of first intestinal surgery are very similar (25,26). Similarily, rates of second surgery for post-operative recurrence did not change significantly through the years 1950-1990, about 35% of the patients had to be re-operated on 10 years after the first intestinal resection (27). However, in the Danish cohort, patients diagnosed in 2003-2004 had a surgical rate significantly reduced when compared to previous cohorts (25). This observation may be the result of the impact of new therapeutic agents.

Indeed, although their onset of action is slow, the immunomodulators azathioprine and methotrexate heal the mucosa (28). Infliximab therapy introduces rapid mucosal healing and is associated with decreased hospitalizations. Both immunomodulators and anti-TNF are effective in maintaining clinical and endoscopic remission with the condition that they are used permanently (29). Although we showed in a previous study (26) that the larger use of immunosuppressants in CD patients was not associated with a decreased surgical rate, this lack of efficacy was probably related to the too long delay of initiation of therapy, at a time when the anatomical lesions had become irreversible. Actually, immunosuppressants in patients who respond to these treatments (about half the patients) do change the disease course, decreasing year-by-year activity and the annual surgical rate from 5 to 2% (Fig. 2). The effect of anti-TNF is visible in patients non-responders to azathioprine or methotrexate, with a significant decrease in activity and surgery throughout the years 2000-2006 (Fig. 2). In total there are some signals of a better control of disease activity and change of natural history during the most recent years, in relation with an earlier and larger use of immunosuppressants and anti-TNF in high-risk patients.

Cancer

The problem of cancer is beyond the scope of this review. There is in most series of colonic CD an increased risk of colon carcinoma, although this was not observed in the Danish cohort study, possibly due to maintenance treatment with 5-aminosalicylic acid preparations and surgery in treatment failure (30). The long term risk of small bowel adenocarcinoma is much increased (more than 50 fold when compared to a background population) and this problem is an increasing challenge. Again, there is the possibility that 5-aminosalicylates and surgery decrease this risk. Finally other malignancies and lymphomas may become more prevalent in the near future in relation with a decrease of intestinal resections and the increased use of immunosuppressants and biologics.

Mortality

In population-based studies, mortality in CD is slightly elevated when compared to general population. A recent meta-analysis using a random effects model showed the pooled estimate for standardized mortality ratio in Crohn's disease was 1.52 (95% confidence interval 1.32 to 1.74). This mortality ratio has decreased slightly over the past 30 years, but this decrease is not statistically significant (31). In other terms, being diagnosed with CD increases of 50% the risk of death in a given interval of time. In the Danish cohort, the excess mortality was observed mainly among women diagnosed before the age of 50 and followed for more than 20 years

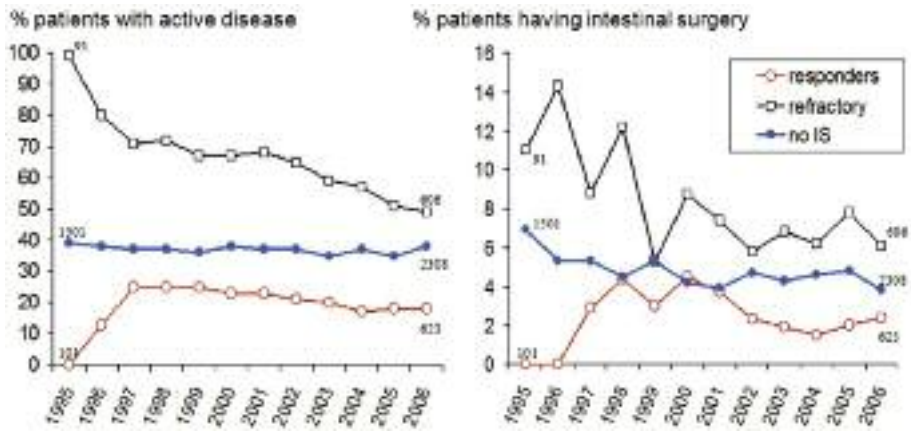

Fig. 2. — Percentage of patients with active disease (left part of the figure) and having intestinal surgery (right part) every calendar year over the period 1995-2006, in three groups of patients defined by their response to first-line immunosuppressive therapy (IS). Responders were defined as patients who were inactive the year following the introduction of IS, and refractory as those who were active the year following the introduction of IS. The year of diagnosis was excluded from analysis. The numbers indicate the number of patients in each group during the years 1995 and 2006, respectively.

after diagnosis. Most deaths were connected with CD : malnutrition, post-operative complications, intestinal cancer. Other causes included respiratory diseases, infections, and diseases of the urinary organs (32). Smoking, more prevalent in CD (33), may explain in part this excess of mortality.

Conclusion

CD is a multiform chronic disease, with onset usually in young adulthood, which continues all life long, inducing progressive and irreversible anatomical damage. The severity of the disease in one individual is poorly predictible at diagnosis, although children and patients with perianal disease are at higher risk of severe disease. As it has been developed in rheumatoid diseases (34), there is a need in CD to develop an index to assess the anatomical damage, taking into account stricture and fistula formation at the different levels of the gastrointestinal tract. This tool may be used to evaluate the true impact of new therapeutic agents on the evolution of the disease.

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