

DIGESTIVE DISEASES

Early and Late Crohn's Disease Are Distinct Entities

Epidemiology of the Transition from Early to Late Crohn's Disease

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Abstract

Phenotypically, the transition from early to late Crohn's disease is characterized by the occurrence of complications including strictures, intra-abdominal fistulas and perianal fistulas, all of them leading to various types of surgeries and currently non-reversible tissue damage. It must, however, be kept in mind that this transition is not at all a uniform and linear process. According to these simple phenotypic criteria, Crohn's disease can already be a late disease at diagnosis while in other patients, it can still be an early disease after 20 years of evolution. This simply highlights the relativity of time in this field, actually reflecting the nature, location and severity of the inflammatory process. The risk over time of the development of these complications has been described, first in cohort studies and then in population-based studies. Globally, at diagnosis, between 19 and 38% only of Crohn's disease patients have complicated Crohn's disease. After 10 years, between 56 and 65% of patients have developed either stricturing or penetrating complications. After 20 years, these numbers are between 61 and 88%. In parallel to these structural changes, changes in the immunobiology of the disease also seem to occur; the latter seem to happen quicker with major modification already within 2 years of the diagnosis. Beside these general figures, important questions remain pending. First, the real timing of these changes is still unclear. Second, the precise role of genetics and environment in the development of these changes remains to be clarified. Third, the correlation between changes in immunobiology and intestinal structural damages has not been specifically studied.

Introduction

In Crohn's disease, the age of the disease does not necessarily correlate with time. Indeed, a late disease, as opposed to an early disease, is characterized by the presence of either stricturing or penetrating complications. The penetrating complication may develop in the abdomen, arising from intestinal loops, or in the perianal region. These complications usually lead to surgical resections, but may develop at different speeds, sometimes already being present at diagnosis in a significant proportion of

patients. Therefore, in Crohn's disease, an 'early' disease can already be a 'late' disease [1, 2]. Changes in the immunobiology of the disease may parallel these structural changes of the intestine, although less data is available on this subject [3, 4]. The relevance of this transition from early to late disease is linked to the fact that it seems to determine a change in response to treatment [5], and beyond this, even a change in the realistic objectives of a treatment strategy, as has been suggested in rheumatoid arthritis [6] and which could be extrapolated to Crohn's disease. In early disease, a deep remission and no tissue damage can be reached, while in late disease only an improvement of symptoms and the healing of lesions is possible. The aim of this article is to report on the epidemiology of this transition from early to late disease. We will describe the number and proportion of patients in the literature who develop features of late Crohn's disease over time, and we will highlight the remaining questions important for a better understanding of the natural history of Crohn's disease.

Cumulative Risk of Complications and Surgery

The development of the stricturing and penetrating complications of Crohn's disease was first described in cohort studies performed in referral centres. In a first study from Liège, according to the Vienna classification, proportions of patients with pure stricturing and penetrating disease (including perianal disease) were 10.8 and 15.5% at diagnosis, 32.2 and 37.2% after 10 years and 32 and 48.8%, after 20 years, respectively [1]. In a simultaneous study on a larger cohort from Paris, similar proportions were found, although a substantially greater proportion developed penetrating disease, with 18% with stricturing disease and 70% with penetrating disease 20 years after the diagnosis, respectively [2]. More recently, a first population-based study reported on the long-term follow-up and development of complications in Crohn's disease. In this study, the Montreal classification was used, excluding perianal disease from the penetrating complication. A slightly lower proportion of patients was shown to develop structuring and penetrating complications with 4.6 and 14% at stricturing diagnosis, 15.2 and 27.5% after 10 years and 21.6 and 37.1% after 20 years, respectively [7]. When adding perianal disease to stricturing and penetrating disease, the overall proportion of patients with such complications reached 60.6% after 20 years. When analyzing the occurrence of perianal complications independently, various prevalences were reported, ranging from 10 to 37% depending on the definition of perianal disease and the time of follow-up [8–10]. In a population-based study from Olmsted County, Minn., the cumulative incidence of perianal disease was below 10% at diagnosis and had reached 26% after 20 years [10]. The stricturing and penetrating complications of Crohn's disease are often indications for surgical resection, which is also a marker of late Crohn's disease. In

Norway, Denmark and a European collaborative study, the rate of surgical resection after 10 years was 38, 55 and 40%, respectively [11–13] . At 30 years, it reached 64% in a population-based study from Olmsted County [14] and was above 80% in the National Cooperative Crohn's Disease study from the USA [15] .

Tissue Damage and Disability as Markers of the Age of the Disease

As highlighted in the previous paragraph, the most relevant impact of time on Crohn's disease may be the development of complications that potentially lead to surgery. Overall, these could be grouped under the term 'tissue damage'. Indeed, it has recently been proposed that the nonreversible cumulative tissue damage is the most relevant outcome that should be measured to assess the real impact of different treatment strategies. A late disease would then be characterized by the accumulation of this tissue damage, and the epidemiology of the standardized measure of it could help us to better define the age of the disease. Hence, an international collaborative research group is currently aiming at validating a standardized score of tissue damage [16] . In parallel to tissue damage, the patient may also develop different degrees of disability. Such a disability score may thus also help to differentiate early versus late disease. With the collaboration of the World Health Organization, a disability score has recently been built up in Crohn's disease [17] .

Changes in the Immunobiology of the Disease

Beside these structural intestinal changes and their consequences, relevant changes in the immunobiology of Crohn's disease may also reflect disease evolution and represent good markers of the disease's age. In particular, a change in T cell polarization and cytokine production has been consistently described [3, 4] . Higher production of interleukin (IL)-12 seems to reflect earlier disease, while later a Th17 profile seems to appear. This change may be much more rapid than the manifestation of structural damage as it occurs mainly within 2 years of the diagnosis. However, so far, no standardized definition of late disease according to these criteria has been proposed, and data on the correlation between these immunobiological changes and the structural damage are lacking.

Impact of the Disease's Age on Response to Treatment

One of the most relevant consequences of disease duration is an apparent decrease in the ability to respond to different drugs including antitumor necrosis factor (anti-TNF) treatment. Different reasons have been proposed to explain this diminished response, including tissue damage and particularly the stricture formation, but also a

change in the immune status of the patients. From this point of view, the transition from early to late Crohn's disease may be more rapid than for tissue damage or disability and may parallel more the immunobiological changes; a significant decrease in the ability to respond to anti-TNF has been described after already 1 year of duration of the disease and even more strikingly after 5 years [5] .

Pending Questions

As highlighted by the previous paragraphs, the amount of data on the epidemiology of transition from early to late Crohn's disease and indeed, on the definition itself of these entities, is scarce. There are currently more questions than answers in this field. In the following paragraphs, we aim to describe the most relevant question and elements of response.

What Is the Real Natural History of These Complications?

There is no study that precisely and prospectively describes the occurrence of tissue damage including fibrosis, strictures or fistulae. These complications are usually diagnosed when they become symptomatic, but the time that has elapsed between active inflammation and the development of these lesions is not known. From experimental models or from other human diseases, including ischemic colitis, we know that it may be very rapid and that a tight stricture does not necessarily reflect a long-standing inflammatory process [18] . It is probable that this process may very much vary from patient to patient depending on their genetic background, the intensity and depth of the inflammation and maybe on environmental factors including the composition of the intestinal flora [19] .

What Is the Correlation between Structural Changes in the Intestine and Changes in the Immunobiology of the Disease?

As stated earlier in this text, we currently do not know if the immunological changes that have been described between early and late Crohn's disease evolve in parallel or may precede and influence the remodeling of the intestine, leading, in turn, to tissue damage and complications.

What Is the Role of Genetics and Environment in the Development of Complications?

Genetics and environment most probably play an important role in the development of Crohn's disease complications and intestinal tissue aging. Besides the factors determining the intensity, location and depth of the inflammation itself, specific factors may influence the inclination to develop fibrotic and/or penetrating lesions. However, very few studies have adequately addressed this very important question. In a large multivariate analysis of a cohort of Belgian patients, the environmental, clinical, serologic and genetic factors associated with the development

of stricturing or penetrating lesions in Crohn's disease were examined. A variant in a gene encoding for a hypothetical protein in the vicinity of the *IL12B* gene in combination with ileal location of the disease was associated with stricturing disease, while male gender together with a single-nucleotide polymorphism in a gene desert of 5p13.1 was associated with internal penetrating disease [20]. In an experimental model, the composition of the flora also influenced the development of fibrosis [19]. The role of genetics and environment regarding other features of the transition from early to late disease, such as changes in immunobiology, microbiology or the ability to respond to treatments, has not been studied.

Can Early and Late Lesions Really Coexist in Crohn's Disease Patients?

Clinical experience shows that early and late lesions may indeed coexist in Crohn's disease. A patient may harbor at the same time an old fibrotic stricture, which has been present for several years (and apparently no longer developing) and more recent lesions not associated with deep-tissue remodeling but rather florid inflammation. However, these florid inflammatory lesions in a patient with long-standing disease may be characterized by a 'late' immunological profile. Postoperative recurrence is another concept-challenging situation: should this be considered as early disease again while the disease has already had complications? The cytokine profile of the mucosa in early recurrent Crohn's disease is clearly different from that of the established lesions [21], but the increase in IL-4 production detected in such postoperative lesions has also been described in late lesions in another study, independently of the postoperative status [3].

Conclusions

The transition from early to late disease is characterized by the occurrence of tissue damage leading to disease complications and disability. It appears in parallel with a change in the immunobiology of the disease and leads to a change in the ability to respond to medical treatment, anti-TNF in particular. This transition occurs at different speeds in different patients, but in the most aggressive disease profiles, it is quick and intense, occurring within 1 year of disease onset. The changes in immunobiology and partly in response to treatment seem to precede tissue damage in the intestine. Much is still to be done to better understand the factors involved in these changes and how our treatment strategies can intervene.

Disclosure statement

The author declares that no financial or other conflict of interest exists in relation to the current article.

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