DigestScience
Digestive tract diseases and nutrition research Foundation

Chronic inflammatory bowel diseases (IBDs)

A scientific enigma…

The chronic inflammation of the digestive tract that characterizes IBDs would appear to be the consequence of an anomaly in the gut immune response with respect to elements of the intestinal flora in genetically predisposed subjects, under the influence of environmental factors.

Genetic predisposition

Genetic predisposition has been suggested for a number of years in light of the high number of persons from certain ethnic groups who have such diseases, the occasional association with genetic diseases, and above all, the observation of familial cases (often with strong similarities in the way the disease presents) and concordance of these diseases among twins. Since 2001, when the first susceptibility gene was identified (NOD2/CARD15 on chromosome 16), nearly 100 other genes have been identified. Taking into account the frequency of these diseases, the absolute risk for first-degree relatives (parents, siblings, children) of contracting the disease is around 1% (compared to 0.1% in the general population), but this rises to 6% if several family members are afflicted. Nevertheless, up until now, there has been no indication for carrying out a genetic survey. Relatives of CD patients are informed of the slightly increased risk and are advised to avoid smoking (smoking is the only risk factor thus far clearly identified) and to rapidly consult in case of digestive symptoms suggestive of the disease.

The role of these genes, their interactions and the consequences of their mutations are currently the object of intense research, but their importance in the physiopathology of IBD remains only moderate. IBDs are not hereditary diseases.

Disruption of the immune system

This is characterized by abnormalities in innate and specific immune responses. The innate immune response is the organism's first line of non-specific immediate defense. A vast series of mechanisms enter into action, associated with an increase in gut permeability, in particular, with respect to bacteria present in the digestive tract that are then capable of inducing inflammation and attracting immune cells in the intestinal wall.

These specialized immune cells induce a specific response toward the constituents of the patient's intestinal flora, thereby maintaining inflammation of the small intestine or the colon.

Role of the environment

Variations in the incidence (number of new cases per year) and prevalence (number of patients) of IBD, both temporally and spatially, suggest a major role for the environment. IBDs are first and foremost environmental illnesses. Epidemiology has demonstrated a higher incidence in industrialized countries and an increase in these diseases in developing countries. This suggests that certain environmental factors, probably linked to the western way of life, might have a substantial influence upon the onset of the disease.

The study of migrant populations is highly interesting and clearly demonstrates that certain populations which initially had low incidences are now tending to rapidly catch up with those of their host country, illustrating the importance of lifestyle in the onset of these diseases.

A number of risk factors have been evoked. The only ones clearly established to date are tobacco (by as-yet-unexplained mechanisms, not linked to nicotine), which protects from UC but promotes and aggravates CD, and appendectomy (during childhood), which protects from rectocolitis.

Influence of the intestinal flora

At present, it is well established that the gut flora or microbiota plays a key role during the course of IBD. Various observations illustrate this:

In patients with IBD, different bacterial populations are modified (dysbiosis). Excess quantitites of potentially pathogenic bacteria are found (including *Escherichia coli, Listeria monocytogenes, Yersinia enterocolitica* and *Mycobacterium paratuberculosis*), but at the same time, the concentrations of beneficial bacteria of the *Firmicutes* group decrease both in number of species and proportions.

The most frequent localizations of the IBDs coincident with zones where the highest densities of bacteria from the digestive tract are found (terminal ileum and colon).

For patients in whom surgery was necessary, risk of early recurrence rises concomitantly with a drop in the concentration of a certain bacterium (*Faecalibacterium prausnitzii*). In animal models of IBD, administration of this bacteria or of the molecules it secretes reduces gut inflammation and sharply improves survival. Likewise, an inflammatory intestinal illness does not develop if animals are maintained in a sterile environment from birth on.

All of these observations open the way to promising research perspectives, development of novel diagnostic tools and new hope for progress in therapy and prevention.

Similarities

IBDs share certain epidemiological, therapeutic and clinical similarities. Their main differences lie in the topography, arrangement and type of lesion in the digestive tract.

- **Ulcerative colitis** is characterized by continuous lesions that begin in the rectum and may spread out in one piece throughout the colon without ever attaining other segments of the digestive tract. These lesions are most often superficial and thus are at the origin of the bright red blood in stools, referred to as rectorrhagia**.**
- **Crohn's disease** can affect the entire digestive tract, from the mouth to the anus. They are segmentary, discontinuous on the affected segments, generally deep and can sometimes cause fissures, fistulas (holes in the intestinal wall) and stenoses.

There exists no cure for these diseases, and no means of prevention. The only existing medical response is limited to controlling the symptoms.

Diseases found at high frequencies

The number of cases of IBD drastically increased in industrialized countries between 1945 and 1980, notably in France and Belgium. They may affect around 2.5 million people worldwide. With a rate of over one out of 1,000 persons afflicted in industrialized countries, France alone has nearly 200,000 cases of IBD. Nearly 6,000 new cases are diagnosed in France each year, amounting to around 17 new cases per day.

The Nord-Pas-de-Calais region, where the DigestScience Foundation is implanted, counts over 16,000 patients. This figure is very high compared to other French regions, and there has been a substantial increase (+29%) over the last few years (1988-2007) in the number of patients with CD and a higher frequency of familial forms.

Young people, a highly affected population

These pathologies most often begin in young adults, with a peak frequency between 25 and 30 years of age. Over 10% of patients are under 17 years of age at the time of diagnosis, representing around 9,000 children and adolescents in France. For CD, a recent Epimad study showed a very clear-cut increase in its incidence (the number of new cases per year) in the 10-19-year-old age bracket, estimated at +70% over the period stretching from 1988 to 2007. For these patients, the disease is

often severe, notably due to the longer duration of evolution during the course of their lifetime. This raises problems in term of specific management, notably for ensuring satisfactory increases in height and weight.

Painful, chronic pathologies

In terms of pain level, IBDs are extremely worrisome. CD and UC evolve via periods of crisis (called flare-ups) that may last from several weeks to several months, interrupted by periods of remission.

During these flare-ups, patients suffer in particular from abdominal pain, chronic diarrhea, permanent fatigue and weight loss. Evolution of IBD is accompanied in one out of 5 cases by extra-intestinal manifestations, often severe, which may reveal the disease, especially at the oral, cutaneous, articular and ocular levels.

The following complications, some of them frequent and some possibly appearing for the first time, complicate medico-surgical management of the disease: severe colitis, fistulas, stenoses and degeneration to cancer, the risk of which is 18 times higher than that of the general population after 20 years of evolution of a pancolic form.

In young children, IBDs induce malnutrition which can cause significant growth delay in terms of height and weight.

Evolutive forms of IBD are part of the long-term pathologies reimbursed 100% by the national health insurance system.

Diseases that remain incurable

At the present time no cure exists. The goal remains the rapid control of symptoms during flare-ups, followed by maintenance of remission via routine treatment. Early recourse to immunosuppressants and the arrival of biological therapy dominated by anti-TNF-α have modified the management and surveillance of these patients.

- **Aminosalicylic derivatives** are very frequently used in UC due to their anti-inflammatory effects, but also for reducing risque of onset of colorectal cancer.

- **Corticoids** are the basic treatment for mild and severe outbreaks. They are used over a short term to limit secondary effects. Corticoids are not effective at preventing risk of relapse and must not be used for maintenance therapy.

- **Immunosuppressants** act by targeting certain components of the immune system. Azathioprine, 6-mercatopurine and methotrexate are most frequently prescribed for routine treatment. Since they take several months to have an effect, they cannot be used alone for treatment at the time of a flare-up.

- **Biotherapy** includes infliximab (European name: Remicade) and adalimumab (or Humira), monoclonal antibodies that neutralize TNF-, an inflammatory molecule that is overproduced during the course of IBD. The treatment can be used during refractory flare-ups, for fistulous types and as routine treatment.

- **Antibiotics** are prescribed for treating proliferation of bacteria in the gut.

- **Antidiarrhetics** slow down the passage of food through the intestine.

- **Antispasmodic agents** combat abdominal pain. Their effect against spasms can take place in nerve fibers, muscle fibers, or both.

- -In addition to the need for an adequately adapted diet, **nutrition treatmen**t via artificial feeding may prove to be necessary. In certain cases, this can lead to remission of evolutive outbreaks (only for CD) and/or ensure (or restore) a satisfactory nutritional status. This type of artificial feeding may be enteral (by nasogastric probe) or parenteral (intravenous) and can be carried out during hospitalization or at home.

- **Surgical treatment** is necessary when there is an unfavorable evolution of the disease or in case of onset of complications (stenoses, fistulas, etc.) This sometimes entails practicing a stoma, which may be temporary or definitive. Unfortunately, surgery is not a definitive treatment for CD. It can, however, lead to a long remission period. Throughout their lives, 3 out of 4 patients will have recourse to surgery. For UC, surgery definitively cures the disease by complete ablation of the colon, referred to as total colectomy.

- **Therapeutic protocols: new hope for patients**. Despite considerable progress over the last few years, a number of diseases defy treatment. These protocols are being carried out with a view toward testing novel alternative therapies, but also for optimizing treatment management programs.