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Review

Diagnostic and treatment difficulties in Crohn's disease

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Abstract

Inflammatory bowel diseases are related to a special pathology having a great psychosocial and economic impact, being represented by chronic diseases which often affects the adult/ active population and that require a long-term treatment. The incidence of Crohn's disease has recorded an increasing trend amongst the general population. However, the incidence of regional enteritis is somewhat lower than in the case of ulcero-hemorrhagic rectocolitis.

The highest prevalence of Crohn's disease is encountered among the populations with a high standard of living; the onset of the disease occurs between 15 and 35 years, but there are also rare cases with onset in childbirth or over 60 years of age. Men and women are approximate equally affected by Crohn's disease.

The main purpose of the treatment is to keep under control the disease, and to increase the quality of life with the following goals: diminishing intestinal inflammatory lesions, relieving symptoms and inducing remission, preventing relapses and complications, as well as maintaining proper nutrition. Appropriate treatment should be adapted to the different clinical-evolutionary forms of Crohn's disease, the succession of different treatment methods being therefore different.

Surgical treatment plays a much more limited role in Crohn's disease than in ulcer-hemorrhagic rectocolitis. Operational interventions are frequently followed by relapses, and surgical resections should be limited to macroscopically affected segments.

Keywords: diagnosis, treatment, Crohn's disease, difficulties

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Introduction

Crohn's disease or regional enteritis is an inflammatory bowel disease with an unknown aetiology, described by Bernard Crohn in 1932. It was originally believed to affect only the small intestine, and was subsequently identified in the colon, too. This disease must be distinguished from ulcerohemorrhagic rectocolitis (another inflammatory idiopathic illness) with which it presents several similarities in respecct to the clinical, anatomopathological, radiological and evolutive characteristics (1).

Inflammatory bowel diseases represent a pathology that has a great psychosocial and economic impact, because they are chronic diseases requiring a long-term treatment on one hand, and affecting the adult population which is active and productive, on the other hand. The incidence of Crohn's disease presents an increasing trend amongst the general population. However, the incidence of regional enteritis is generally lower than in the case of ulcerohemorrhagic rectocolitis (2).

Crohn's disease is a multifactorial affection, being suspected a combination of environmental, immunological and bacterial factors, especially to a category of persons who are genetically susceptible. The patients present a chronic inflammatory status, several components of immune system attacking the gastrointestinal tract in close relation with microbial antigens. Immunological mechanisms involved are not clarified in detail yet, being identified a clear immunodeficiency status but without to imply autoimmune reactions. Smokers are two times more likely (than tobacco nonsmokers) to develop in time Crohn's disease. In addition, more than 70 genes were identified and linked to Crohn's disease, about half of the overall risk being therefore related to such genetic factors (3).

Diagnosis of Crohn's disease is founded on clinical signs and symptoms, appearance of the bowel wall at colonoscopy, medical imaging such as barium enema and biopsy. Crohn's disease is not a curable disease, medications and stopping of smoking (among those who do) being necessary for amelioration of clinical symptomatology, maintaining of remission and thus preventing of relapses. Surgical procedures are generally necessary to address several localizations of abscesses, the occurring bowel obstructions, and malignant degeneration (4).

Discussion

Crohn's disease is characterized by several transmural granulomatous lesions (with discontinuous distribution), which are located at any level of the digestive tract (but predominantly at the terminal ileum), being accompanied by extradigestive/ systemic manifestations. Inflammation may be limited in some cases especially to the small intestine or only to the colon, the latter posing serious problems of differential diagnosis with ulcerohemorrhagic rectocolitis (5).

Epidemiology

The highest prevalence of Crohn's disease is among the populations with a high standard of living (Western Europe and North America), with a frequency of 2-5 times higher in the white race. The onset of the disease occurs between 15 and 35 years, but there are also rare cases with onset in childbirth or over 60 years of age. Men and women are approximate equally affected (6).

Family aggregation is well documented, with only a 15-30% match in monozygous twins suggesting the important role of environmental factors (dietary, behavioral, etc.) in the onset of Crohn's disease. Smoking are considered to have a double risk of

developing this condition while smoking abstinence decreases the severity of the cramps.

Etiopathogeny

Recent studies investigating the genetic causes of Crohn's disease identified the existence of numerous defects in the intestinal mucosal immune system, linked to the modulation of the nonspecific immune response. This nonspecific immune response may be induced by a variety of infections or intestinal toxins, and may cause its action to increase mucosal permeability, thereby increasing the absorption of toxins in the intestinal lumen (7, 8).

One of the most prominent events in this form of inflammation is the elevation of interleukin 12 (IL_{12}) levels, with the consequent increase in gamma interferon and TNF-alpha production. Unlike normal individuals where these effects are promptly inhibited by allowing rapid healing and sequelae, in the case of genetically susceptible individuals, the immune cascade amplifies symptomatology. This genetic predisposition is related to both Crohn's disease and ulcerohemorrhagic rectocolitis, even if the mechanism of action and the antigenic stimulus appear to be different (9).

Pathological anatomy

Colon injuries are found in about 25% of cases, being usually associated with ileal lesions (in 30% of the cases only the right colon being affected). Segmental colic lesions are usually separated by healthy colic areas, but there are also cases where the colon is entirely affected. Rectal pure forms are very rare, requiring systematic control of the entire colon.

Macroscopically, the wall of the colon appears thickened, congestive, edematous and often fibrous, such phenomenas leading to the formation of stenoses which are accompanied by mesothelial sclerolitis and regional adenopathy (10, 11).

During the opening of the colic mucosa there is found the headquarters of ulcer, as round and well defined aftoid ulcers, which have hiperemic halos that are separated from each other by the mucous membranes. With time, they merge and fuse to become linear, in the form of intersecting tracts delimiting ulcers between normal tissue areas (pavement stone). The cracks can go deeper even beyond the intestinal wall, causing occurrence of several fistulas.

Microscopically, the infiltration of lymphocyte-plasmocyte and massive collagenation encompass all the intestinal wall layers, within time leading to even stenosis. The characteristic lesion is sarcoid granuloma, present in both the intestinal wall and adjacent ganglia. It is a complex of epithelial cells and giant multinucleated cells surrounded by a peripheral lymphocyte nucleus. Axonal necrosis of autonomic nerves represents an early histological lesion, characteristic of Crohn's disease (12).

Diagnosis

The clinical appearance of Crohn's disease varies depending on the location and extent of the lesions. Vienna classification tries to identify possible patterns of disease progression, taking into account the onset of disease, localization of lesions and the presence of complications. It has thus been observed that the onset of early disease is associated with a larger extension of the small intestine, the appearance of stenoses and the need for repeated surgery.

The disease onset is often insidious, with intermittent diarrhea that has a low volume in colonic forms (possibly with tenesms and imperative evacuations) or moderate in small intestine (5-6 evacuations/ day, aqueous, explosive, with steatoree in ileo-colonic localizations). Diarrhea is accompanied by diffuse pain (vagal) that usually precurses defecation and improves afterwards. Rectoragy may be present, but without gulles or pus. Perianal lesions are chronic, recurrent and multilevel, which requires a biopsy to

diagnose the disease. In some cases, the diagnosis is established after few years from the initial onset of the disease, due to the fact that the symptoms appear gradually and are not severe in the beginning stages, and because it is usually affected only a limited portion of the intestine (13, 14).

Systemic manifestations occur more frequently in Crohn's disease than in ulcerohemorrhagic rectocolitis and consist of weight loss, asthenia, meteorism and fever. The disease associates a series of extraintestinal expressions such as cutaneous and mucosal manifestations (erythema nodosus, stomatitis), ocular (irritated, uveitis), osteoarticular (enteropathic arthritis, osteomalacia), and hepatobiliary (autoimmune chronic hepatitis, sclerosing cholangitis).

The clinical examination may be suggestive or eventually indicate a massive abdominal tumor with inflammatory appearance, parietal fistulas and ano-perianal fistulae (which may sometimes represent the first sign of the disease). Nutritional deficiencies can be encountered and are the result of inflammation and intestinal lesions, which often lead to a poor intestinal absorption for food (15).

The paraclinical examinations are related to anemia, electrolyte disturbances, hypoproteinemia, increased inflammatory evidence, and thrombocytosis in the active forms. In the presence of suspicion of Crohn's disease, complete colonoscopy with terminal ileon biopsy may indicate the diagnosis. Small endoscopic video tapes can be used to evaluate the small intestine. Ultrasound and computer tomography highlight the marking of the terminal ileum and the check, and are useful in the early diagnosis of complications.

Barium enema reveals discontinuous, staggered lesions that associate lacunae and ulceration. Initially there are predominantly marginal blurry images, evolving in the form of a button to become afterwards fistulas. In late stages there appear stenoses that may evolve towards occlusion. Simple abdominal radiography can monitor the appearance of intestinal occlusion, as seen in the image of alveolar, toxic megacolon or pneumoperitoneum (16, 17).

Tc 99-labeled leukocyte scintigraphy allows not only the localization of lesions but also the extent and severity of the inflammatory process (due to accumulation of neutrophils in the inflamed tissue). Coprocitologic tests are useful in the differential diagnosis of Crohn's disease, excluding thus other intestinal disorders with similar symptoms.

Evolution and complications

The evolution of the disease is variable and unpredictable, from light forms that can be treated by medications to dramatic/ overactive forms. It is dominated by relapses that can occur at variable intervals. These often occur after successive surgical interventions, the remaining colon being sometimes insufficiently for digestion (18).

The course of the disease can be challenged by a series of complications - intestinal occlusion (often occurring in the terminal ileum), intraabdominal abscesses, internal fistulae (entero-enteral, enterocolitic, vesicular, colo-vaginal) or external (more frequently in ileal localizations). The fulminant colitis, the toxic megacolon, the major rectoragies are also possible complications but they however occur much less frequently than in ulcero-haemorrhagic rectocolitis.

People diagnosed with Crohn's disease for more than 10 years should be integrated into a screening program (early detection) of small intestine and colon cancer, due to an increased risk for developing the malignant complication. Systemic complications occur in 70% of cases. Some evolve simultaneously with the emergence of digestive disease (nodular erythema, migratory arthritis, anterior uveitis, venous

thrombosis), others independent of it (amyloidosis, pericolangitis, and sclerotic primitive colangitis) (19).

Treatment

The prophylaxy of Crohn's disease can not be performed, because until now the etiopathogenesis of this condition is not fully elucidated. There are several factors that can decrease symptomatology reducing thus the severity of the condition, such as stopping smoking and respecting a hygienic-dietary and healthy lifestyle. The main purpose of the treatment is to control the disease and increase the quality of life with the following goals: diminishing intestinal inflammatory lesions, relieving symptoms and inducing remission, preventing relapses and complications as well as maintaining proper nutrition. Appropriate treatment should be adapted to the different clinical-evolutionary forms of Crohn's disease, the succession/ hierarchy of different treatment methods being therefore different.

The symptomatic treatment follows correction of hydroelectrolytic disorders, antispasmodic and analgesic administration in cases of pain, treatment of diarrhea with loperamide or cholestyramine. In the case of patients with long symptomatology/ episodes, a hypercaloric diet and exogenous intake of vitamins (B_{12}) and iron may be required (20).

Moderate forms of Crohn's disease but with persistent symptomatology require administration of aminosalicylates, such as Sulfasalazine and Mesalazine (4g/day). These drugs are effective in most cases, especially in those with coexisting lesions in the colon. Corticosteroids (Hidrocortizon, Prednison) can be administered to reduce intestinal inflammation. However, such drugs are not recommended to be administered over extended periods of time (months or years), due to undesirable side effects (hypertension, osteoporosis, susceptibility to infection, infertility, diabetes). Serious forms benefit from intravenous administration of costicosteroids.

Severe and persistent symptomatology requires administration of immunosuppressive medication, and also parenteral nutrition. Immunosuppressants used usually in Crohn's disease are represented by: Azathioprine, 6-mercaptopurine and Methotrexate. These drugs are given when aminosalicylates are not tolerated, when aminosalicylates are ineffective in relieving symptoms, or when discontinuing the corticosteroid treatment determines the recurrence of the symptomatology (21).

Biological therapy with Infliximab appears to be effective but should be used with caution in patients with suggestive obstructive symptoms. Antibiotics (more commonly used in the form of metronidazole and ciprofloxacin) are particularly effective for distal localized (perianal) or fistular localization, but long-term use is not recommended due to potentially adverse side effects. Surgical treatment plays a much more limited role in Crohn's disease than in ulcer-hemorrhagic rectocolitis. Surgical interventions are frequently followed by relapses, so that resections should be limited to macroscopically delineation of affected segments.

Conclusions

Treatment options for Crohn’s disease are currently evolving and increasing in complexity. There is a potential risks for undertreatment and over-treatment with immunomodulators and/ or anti-TNFα therapy. The anti-TNFα therapy is effective for severe cases, so that this form of therapy should be maintained for selected patients. Operatory indications for Crohn's disease are represented by acute complications (perforations, uncontrolled drug bleeding or severe acute life threatening). Elective surgical interventions target the chronic uncontrolled forms through medications, and pancolite with over 10 years of development, usually with severe intestinal dysplasia or malignant transformation (22).

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