The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

EASi™
European Autoimmunity
Standardisation Initiative


ThermoFisher
SCIENTIFIC

The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Inflammatory bowel diseases

Nathalie Vermeulen, Xavier Bossuyt, Paul Rutgeerts, Severine Vermeire

1 Introduction

Inflammatory bowel disease (IBD) is a general term for a heterogeneous group of gastrointestinal diseases, including Crohn's disease (CD) and ulcerative colitis (UC). Both disorders are life-long with periods of remission and relapse. CD is characterized by an asymmetric and segmental transmural inflammation which may affect any part of the gastrointestinal (GI) tract. In 30 % of cases, the site of inflammation is the small bowel (Crohn's ileitis). Twenty percent of cases show inflammation of the colon only (Crohn's colitis). In 50 % of cases, inflammation of the ileum and the colon is found (Ileocolitis). Upper GI involvement in the oesophagus, stomach, duodenum or jejunum can coincide with all 3 locations. The disease behaviour can be stricturing, penetrating or neither [1].

UC, on the other hand, is characterized by a diffuse mucosal inflammation which is limited to the colon. Depending on the extension, the sub phenotypes of UC are proctitis, left-sided colitis and pancolitis, with the inflammation limited to the rectum, extending to the flexura sinistra, and involving the total colon, respectively. Many similarities exist between CD and UC, leading to the lack of a definite diagnosis in approximately 10 % of patients with colon-limited IBD. These patients are (temporarily) diagnosed with colitis-type unclassified or indeterminate colitis [2] (Table 1).

IBD is most often diagnosed in patients between 15 and 30 years, with a second incidence peak at ages above 40.

The pathogenic causes of IBD are still unknown. It is hypothesised that IBD is an immunologically mediated disorder in a genetically susceptible host. IBD is thought to result from an inappropriate and ongoing immune response and loss of tolerance to the normal luminal flora. This aberrant response leads to chronic inflammation of the gut and is most likely facilitated by defects in barrier function of the intestinal epithelium and the mucosal immune system.

IBD occurs worldwide, but a markedly higher incidence is observed in the industrialised areas of the world (Europe and the USA). The average annual incidence of CD in Europe and North America is rising and is estimated at

Table 1. Structural distinctions between ulcerative colitis and Crohn's disease.

Ulcerative colitis	Crohn's disease
Rectum ± colon	Mouth to anus
Continuous	Discontinuous
Mucosal	Transmural *(fissure, abscess, fistula)*
Muscular thickening	Fibrosis (stenosis)
Mucin depletion	Lymphoid ulcers, aggregates
Glandular damage	Granuloma (50–70%)
pANCA antibodies	ASCA antibodies

5–10/100 000. The annual incidence of UC is estimated at 10–20/100 000. The prevalence of CD and UC is between 200 and 500 per 100 000.

2 Diagnostic measurements for experts

Diagnosis of IBD is mainly based on eliminating other possible causes of the symptoms including (bloody) diarrhoea and severe abdominal pain. There is no gold standard, but the diagnosis mainly depends on a combination of endoscopic, histological, radiological and/or biochemical examinations.

Initial laboratory investigations usually include markers for acute or chronic inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), anaemia (haemoglobin level, complete blood count), fluid depletion and signs of malnutrition/malabsorption (electrolyte abnormalities). Stool samples should be collected for microbiological testing. IBD-specific antibody tests include the detection of antibodies to autoantigens and microbial antigens. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are antibodies directed to neutrophils that are detected in the serum of 60 to 80 % of UC patients, but also in 5–25 % of CD patients. Antibodies against *Saccharomyces cerevisiae* (ASCA) are detected in 50 to 80 % of CD patients, and in less than 10 % of UC patients. However, at present, these autoantibodies are not routinely screened for in patients suspected of IBD because of their moderate sensitivity and specificity.

To establish the diagnosis in patients suspected of CD, ileocolonoscopy with biopsies of the ileum and colon for microscopic examination is the preferred pro-

cedure. In case of severe, active disease, flexible sigmoidoscopy is safer and better to prevent bowel perforation. A plain abdominal radiograph is valuable in the initial assessment of possible bowel dilatation, calcified calculi, sacroiliitis or the impression of mass in the right iliac fossa. Fluoroscopic examinations (small bowel follow-through, small bowel enema) are the current standard for assessing the small intestine. Barium studies can be helpful, but they are subject to several factors that can influence the quality of the result. Computed tomography (CT), mostly performed in severe cases, provides additional information on bowel thickening, changes in vascularity and mesentery. In case of obstruction or bowel narrowing, small bowel enema and double contrast enema are the procedures of choice to assess disease extent and location. For detection of extramural complications (fistula or abscess), ultrasound, CT and magnetic resonance imaging (MRI) can be performed. Histological examination of endoscopic biopsies searches for signs of patchy chronic inflammation, focal crypt irregularity and granulomas, as these are the generally accepted microscopic features of CD. In ileal samples, irregular villous architecture can be detected [1].

To establish the diagnosis in patients suspected of UC, colonoscopy, preferably with ileoscopy and segmental biopsies, is the procedure of choice. In case of a severe attack, abdominal radiography and sigmoidoscopy are recommended. Other techniques that can be used to asses (the severity of) UC, including hydrocolonic ultrasound, Doppler ultrasound, virtual colonography, leukocyte scintigraphy are of secondary value in the diagnosis of UC. Histological examination of endoscopic biopsies reveals basal plasmacytosis (presence of plasma cells around or below the crypts), an increase in heavy, diffuse transmucosal lamina propria cells and widespread distortion of the mucosa or crypt architecture. These features indicate UC [2].

3 Requirements for family practitioners

IBD are chronic diseases with periods of active disease and remission. Symptoms heavily depend on disease activity (remission or active disease), but also on the subtype of IBD (UC or CD), and the severity of the disease (Table 2).

Medical history of a patient should include questioning about the onset and recurrence of symptoms, including rectal bleeding or bloody diarrhoea, abdominal pain, urgency, nocturnal diarrhoea. Furthermore, smoking habits, recent travel, food intolerance, recent medication, and family history should be explored.

Physical examination should evaluate general well-being, pulse rate, body temperature, blood pressure, body weight, abdominal examination for distension and tenderness, oral inspection and check for extraintestinal manifestations, including ocular, oral, joint, or skin lesions. However, physical evaluation may be normal in case of mild or moderate disease. Strongly suggestive symptoms include bloody

Table 2. Signs and symptoms of the disease.

	Crohn's Disease	Ulcerative Colitis
Intestinal symptoms	Abdominal pain and cramping	
	Persistent diarrhoea	
	Perianal disease	Blood in the stool
	Loss of appetite	Rectal tenesmus
	Fissures*	Faecal urgency/ incontinence
Non-Intestinal Symptoms	Fever	
	Malaise	
	Anorexia*	
	Arthropathy*	
	Weight loss	Episcleritis*
	Delayed growth in children	Erythema nodosum*
	Eye irritations*	

* Symptom found in a minority of cases

diarrhoea lasting for more than 1 week, non-bloody diarrhoea lasting for more than 3 weeks, or severe abdominal pain with significant weight loss.

Initial laboratory testing should include complete blood count, electrolyte, blood urea nitrogen, creatinine, liver enzymes, iron studies, and CRP. Furthermore, examination of stool samples could eliminate the presence of infectious agents.

For definite diagnosis, medical history and physical examination should be complemented with endoscopy and/or histological findings in segmental biopsies. Rapid awareness of possible IBD and referral to a specialist for endoscopy can significantly decrease the time to diagnosis and therefore improve the prognosis of the patient [1, 2].

4 Follow up

Clinical observations

During treatment, symptoms gradually improve and patients reach clinical remission. Treatment is, if possible, gradually decreased to avoid dependence and/or intolerance.

Expectations

IBD patients have variable prognosis; some patients reach remission and remain in remission for several months or years, while others never reach a state of remission. If treatment fails to induce remission, surgery can be an option. Most CD patients will eventually have surgery. One in 4 UC patients will have surgery within 10 years of diagnosis. Patients with extensive disease (pancolitis) have a higher risk for surgery. Patients with severe disease have increased risk for developing colon cancer.

Blood tests

Routine laboratory tests, including C-reactive protein determination, can be used to evaluate the response to treatment and to assess clinical improvement. Normalisation of routine laboratory test values and relief of symptoms are indicative of remission. However, complete clinical remission is defined by complete resolution of symptoms and endoscopic mucosal healing in UC patients, and as a drop in Crohn's disease activity index (CDAI) to < 150 in CD patients. Complete clinical remission must be assessed by a thorough clinical exam and endoscopy.

5 Management

The main treatment for IBD aims at inducing and maintaining a state of remission. For each patient, the most effective treatment is determined by considering the disease activity, site of inflammation, disease behaviour, response to previous medications and the preferences of the patient. IBD is mostly treated with aminosalicylates (mesalazine, sulfasalazine), corticosteroids, immunomodulators (thiopurines (azathioprine, mercaptopurine), methotrexate, cyclosporine, tacrolimus) and/or biological therapies (anti-TNF antibodies (Infliximab, Adalimumab)).

Budesonide, a corticosteroid, is the preferred treatment for mildly to moderately active CD. Severe disease should be treated with systemic corticosteroids, possibly complemented with azathioprine/mercaptopurine in case of a relapse, or methotrexate in case of azathioprine/mercaptopurine intolerance. In case of dependence or intolerance to corticosteroids and/or immunomodulators, Infliximab or adalimumab can be added, but surgery can also be an option [3].

In mild to moderate UC, mesalazine is the preferred initial treatment, topical and/or oral. Severe UC should be treated in the hospital with intravenous corticosteroids. Immunomodulators should be started in steroid-dependent or steroid-refractory patients. Patients dependent or intolerant to corticosteroids and/or immunomodulators could be treated with biological therapies. If the disease persists, surgery is an option [4].

The treatment options described here are considered the standard treatment. However, treatment has to be evaluated for each patient.

6 Diagnostic tests

The presence of pANCA antibodies in the serum of patients is evaluated by means of indirect immunofluorescence with neutrophils as a substrate. Three distinct staining patterns can be detected; a cytoplasmic staining pattern, a perinuclear staining and an atypical perinuclear staining, characterized by a broad inhomogeneous labelling of the nuclear periphery along with multiple intra-nuclear fluorescent foci. The atypical perinuclear staining pattern (atypical pANCA) is found in 60–80 % of UC patients and in 5–25 % of CD patients.

The presence of ASCA antibodies in the serum of patients is evaluated by means of Enzyme-linked immunosorbent assay (Elisa). These antibodies are detected in 50–80 % of CD patients, compared to less than 10 % of UC patients and less than 5 % of the controls.

Other antibodies described in IBD are antibodies to pancreas, anti-OmpC (E. coli) antibodies, anti-I2 (pseudomonas fluorescens) antibodies, anti-CBirI (Clostridium) antibodies and several anti-glycan antibodies (ACCA, ALCA, AMCA). These antibodies still need confirmation and are currently only used in experimental settings [5].

7 Testing methods

Several limitations are associated with pANCA/ASCA testing for IBD. Both antibodies have relatively low sensitivities and specificities, which makes them less accurate in diagnosis of IBD. Furthermore, pANCA is detected with indirect immunofluorescence, which is associated with high interassay and interobserver variability. Therefore, pANCA and ASCA are not routinely tested in every patient suspected of IBD [5].

References

[1] Dignass A, Van Assche G, Lindsay JO, et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010; 4: 28–62. Erratum in: J Crohns Colitis 2010; 4: 353.

[2] Stange EF, Travis SP, Vermeire S, et al. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. J Crohns Colitis 2008; 2: 1–23.

[3] Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. J Crohns Colitis 2010; 4: 7–27.

[4] Travis SP, Stange EF, Lémann M, et al. European evidence-based Consensus on the management of ulcerative colitis: Current management. J Crohns Colitis 2008; 2: 24–62.