INTRODUCTION

Functional gastrointestinal disorders (FGD) are a group of syndromes defined as variable combinations of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. They are classified according to the international Rome criteria for which the 3rd edition has recently been published (1). The most common and best studied among this broad range of disorders are functional dyspepsia (FD), affecting mainly the upper gut, and irritable bowel syndrome (IBS) affecting the intestine. IBS represents the most frequent reason for consultation with a gastroenterologist in the United States (2), its overall prevalence ranging from 3% to 25% (3). The pathophysiology of IBS most likely results from a combination of psychosocial factors, altered gastrointestinal motility and increased sensitivity (4,5). The etiological factors are obscure, but an altered function of the gut neuromuscular apparatus due to previous or ongoing inflammatory events seems likely (6).

Inflammatory bowel disease (IBD) comprises Crohn’s disease (CD) and ulcerative colitis (UC) and is thought to arise from inappropriate and ongoing activation of the gastrointestinal mucosal immune system driven by the presence of normal flora in genetically predisposed subjects (7). The main clinical features are fever, abdominal pain, diarrhea, rectal bleeding, weight loss and malnutrition. Therapeutic efforts are mainly anti-inflammatory or immunomodulatory and aimed at inducing remission.
Gut inflammation is capable of modulating the morphology and function of enteric nerves and smooth muscle cells during the inflammatory episode but also in periods of remission (8). The pathophysiological mechanisms underlying these disturbances have been extensively studied but remain incompletely understood.

**FGD IN IBD: EPIDEMIOLOGY**

Patients with IBD often suffer from gut motility and/or sensitivity disturbances which resemble IBS or can be classified as such (9). Simren, et al looked at IBD patients in remission and found that 33% of UC patients and 57% of CD patients had “IBS-like” symptoms, which was two to three-fold higher compared to a control population (10). Thirty-three percent of patients with UC in remission fulfilled the contemporary Manning criteria for IBS compared to 7% in a healthy control population (11). A recent study confirmed this higher prevalence of IBS during UC in remission using Rome II criteria (12). Health-related quality of life in these patients was comparable with the poor quality of life during active UC. In a Canadian study, 81.9% of Canadian IBD patients in remission had symptoms suggestive of more than one FGD according to Rome II criteria (13). IBS was more frequent in CD patients (26% versus 12.1%) and functional constipation in UC (26.2% versus 14.9%) (13). Several studies confirmed that FGD contribute significantly to overall morbidity and quality of life issues in IBD (10,12,14).

In the very early stages of disease, the occurrence of functional symptoms in otherwise asymptomatic IBD patients can be misleading. In patients initially diagnosed with IBS, there was a documented increased risk of detecting IBD after a maximum of three years (15). IBD should be considered especially in diarrhea predominant IBS-like syndromes presenting with perianal soreness or features such as arthralgia, mouth ulcers or eye signs (16).

Functional gut disease can aggravate the malnutrition and anorexia which often complicate IBD (17), and may jeopardize the efficacy of oral therapy. In this context, it should be mentioned that some of the medications prescribed for IBD patients can also induce FGD-like symptoms. Azathioprine, sulfasalazine, 5-aminosalicylic acid and metronidazole may cause nausea, vomiting and dyspepsia. Another confounding factor is the common occurrence of small bowel bacterial overgrowth, especially in CD (18,19). This can be both cause and consequence of gut dysmotility and needs appropriate and distinct treatment.

**FGD IN IBD: CLINICAL MANIFESTATIONS**

**IBD and Motility Disturbances**

During an inflammatory episode of IBD, motility is altered predominantly towards diarrhea (hypersecretion and enhanced fasting colonic transit (20,21)) with a consequent increase in stool weight and frequency (22). Studies of colonic contractility and motility in patients with IBD showed a reduction in contractility (23,24), a reduction in spontaneous contractions (25), increased low-amplitude propagation and variably affected colonic transit (26). Diminished contractility leads to lower resistance to luminal transit and in combination with secretory disturbances to diarrhea (27). Secretory anomalies in IBD are mostly due to changes in epithelial barrier function and absorption of electrolytes rather than to changes in enteric regulation (28). It can be suggested that diarrhea in IBD is mainly caused by an increase in colonic secretion and/or a decrease in reabsorption, and that the decrease in contractility allows accelerated passage of the increased intraluminal contents. There is less evidence for a real power propulsion response, as is the case in infectious enteritis. In contrast to the impaired contractile responses found in the inflamed colon, small intestinal contractility appears to be enhanced in human CD specimens (29). Using breath tests, orocecal transit was significantly decreased in CD patients with both colonic and ileal involvement (30,31).

There is no convincing data on the occurrence of motility disturbances in the postinflammatory phase of IBD. One study found no differences in 24 h colonic manometric recording between healthy controls and patients with UC in remission (32). Likewise, colonic distribution of a labeled meal was similar in UC patients in remission and controls (22).

Dysmotility can also occur at a level distant from the inflamed region of the gut, suggesting that inflammation in IBD may lead to a modification of general gastrointestinal motor behavior. In 1965, Manousos described a delay of small intestinal motility in
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patients with UC (33). This was confirmed in 62 UC patients who showed an increase in orocecal transit time in combination with cecal and proximal colonic stasis and rectosigmoid irritability accounting for diarrhea (34). Grill, et al reported gastric emptying disorders in malnourished children with CD (35). Most of these cases (75%) had nonconstrictive duodenal involvement, suggesting a role for impaired antroduodenal coordination. Similar results were obtained in adult CD patients without gastric or duodenal involvement (36). Gastric emptying was impaired only in patients with upper gut symptoms (bloating, early satiety, abdominal distension) and/or colonic involvement. Using the cross-sectional antrum area measured by ultrasonography as a surrogate marker for gastric emptying, Kohno, et al described gastroparesis in CD patients with inflammation restricted to the small or large intestine (37). This was accompanied by a decrease of postprandial activity in the electrogastrogram. These papers suggest that Crohn’s colitis has a direct or indirect inhibitory effect on gastric motility, a phenomenon which has also been described and studied in an animal model for CD (38,39).

Gastroparesis can be identified in CD in remission as well. One recent case-report discussed five female patients with inactive CD and scintigraphically confirmed gastroparesis of a histologically normal stomach (40). The symptoms of persistent nausea, early satiety, vomiting and weight loss in these patients were both severe and refractory to drastic therapeutic intervention, indicative of the clinical importance of IBD-associated gastroparesis. Annese, et al found abnormal antroduodenal motor patterns in 26 of 35 (75%) patients with CD in remission (41).

IBD and Sensitivity Disturbances

IBD patients also suffer from visceral sensitivity disturbances, although the evidence is scarce and somewhat conflicting. In patients with active UC, thresholds to first perception of intrarectal balloon distension and to maximal tolerance were significantly reduced compared to controls, which could explain the frequent and urgent defecation in these patients (22,42). This rectal hypersensitivity was accompanied by an increase in tone, which could imply that its mechanism is at least partly muscular in origin (43). During remission, a decrease in rectal sensitivity and an increase in compliance was described (22). On the other hand, others identified visceral hyperalgesia in children with quiescent CD and abdominal pain (44). In a study comparing responses to sigmoid distension between IBS and UC patients, rectal perception was attenuated in mild ongoing UC but enhanced in IBS (45). A possible explanation for the lack of hyperalgesia in patients with chronic active IBD could be the activation of compensatory descending inhibitory pathways, counteracting visceral hypersensitivity (46). Two studies showed that in patients with ileal CD but without proctitis in the history or at the time of the experiment, thresholds for discomfort were significantly increased (47,48) and the recto-anal inhibitory reflex was delayed or absent (48). This is suggestive of sensitivity alterations at sites remote from the inflammation. Bernstein, et al supported the notion that descending bulbospinal inhibition triggered by ongoing inflammation was responsible for these effects (47). Opposing the concept of descending inhibitory control, Galeazzi, et al described esophageal hyperalgesia in patients with UC (49). Thus, it appears that IBD will induce hyper- or hyposensitivity depending upon the degree/duration of inflammation and the subsequent activation of descending inhibitory mechanisms.

FGD IN IBD: MORPHOLOGICAL FEATURES

Inflammatory gross changes of the enteric nervous system found in specimens from IBD patients include nerve fiber hypertrophy and hyperplasia, damage and hyperplasia of neuronal cell bodies and enteric glial cells (8). In about 50% of both CD and UC patients undergoing surgical resection of intestine, lymphocytic ganglioneuritis could be identified in both inflamed and healthy regions of the gut (50).

In patients with CD, the neurochemical coding of myenteric ganglion neurons was altered: increased immunoreactivity of the inhibitory neurotransmitters vasoactive intestinal peptide (VIP), nitric oxide synthase (NOS) and pituitary adenylate cyclase-activating polypeptide (PACAP) was reported (51). Patients with Crohn’s disease showed an increase in vasoactive intestinal polypeptide (VIP)-containing nerves both in the inflamed (continued on page 15)
gut wall and at sites remote from the inflammation (52,53). Schneider, et al noted an increase in the number of VIP-positive neurons as well as a pronounced thickening of calcitonin gene-related peptide (CGRP)-fibers in the rectum of Crohn’s disease patients with ileal and/or cecal CD, even though there was no history of anorectal surgery or endoscopic evidence of proctitis (54).

In both inflamed and normal colon specimens obtained from CD and UC patients, mucosal neuropeptide expression was upregulated (55,56). In UC patients, an increase in Substance P-containing nerve density was described at different stages of inflammation, while the overall nerve density was not different from healthy colon samples (57). Neunlist, et al reported that in whole mounts of the colonic myenteric plexus of UC patients, remodelling of enteric nerve circuits had occurred, generating a shift from mainly cholinergic to more Substance P-mediated innervation (58). These findings are in agreement with the theorem that in pathophysiological settings, the tachykinergic (SP-mediated) contribution to gut motility/sensation is enhanced (59).

An important component of the gastrointestinal neuromuscular apparatus is represented by the interstitial cells of Cajal (ICC), which are involved in the pacemaker generation of spontaneous rhythmic gut contractility. The number of ICC in the small intestine of CD patients was significantly reduced (60). Ohlsson, et al confirmed the CD-associated reduction of both quality (atrophy and vacuolization) and quantity of ICC in the healthy small intestine. In the colon, there was no change in the number of ICC, but their appearance was described as hyperplastic for both CD and UC specimens (50). One can also find alterations in the extrinsic innervation of the gut, where especially the upregulation of TRPV1- and P2X3-receptors deserve attention (61,62). These receptors are involved in the pathophysiology of visceral hypersensitivity.

Finally, but importantly, there are numerous reports on the effects of IBD on the number and function of gastrointestinal serotonin-predominant enterochromaffin cells. In general, there was an increase in the number of these cells both during active inflammation (63) and in periods of remission (64). The increase in serotonergic signaling resulting from this hyperplasia could contribute to inflammation-induced FGD.

**FGD OR IBD: CLINICAL DILEMMAS**

When a patient suffering from IBD presents with functional complaints, the clinician first needs to decide whether the complaints are caused by an acute inflammatory flare, or whether the symptoms could be considered as FGD in an IBD patient in remission. If the former is the case, there is no discussion that the first goal should be to treat the underlying inflammation using combinations of therapeutic agents such as 5-ASA, corticosteroids, immunomodulators or biologics. One should monitor gut motility in this setting as well, since gastroparesis may hinder the delivery of orally administered medication. However, when the patient shows no overt signs of an acute flare, the physician has to decide to consider this as insidious inflammation and treat accordingly using rather aggressive and sometimes expensive drugs, or to consider it as FGD and treat as such using the limited pharmacological tools available while risking the possibility to miss or prevent full-blown inflammation. The discussion emphasizes the great need for a reliable marker of inflammation in IBD, with optimal sensitivity and specificity and capable of predicting relapse. C reactive protein (CRP) is a specific marker for CD activity and correlates well with response to anti-inflammatory therapy, but it is far from ideal and is less sensitive for UC activity (65). An optimized, highly sensitive CRP assay could be a powerful tool to distinguish non-IBD-IBS from active IBD (sensitivity 100%, specificity 67 % for a cutoff of 2.3 mg/l) (66). Another promising marker of inflammation is fecal calprotectin, a neutrophilic protein which is consistently elevated in patients with active IBD. Preliminary studies indicate that this assay is a useful predictor of relapse in patients with quiescent IBD, although the studies were rather small and the specificity of the test appeared higher for UC than for CD (67,68). In addition, it was shown that fecal calprotectin is possibly superior to CRP in distinguishing IBD from non-IBD IBS (69). The latter study reported a sensitivity of 90 % and a specificity of 83 % of calprotectin for predicting relapse in IBD with a cutoff of 50 mg/l. Larger trials addressing these issues and examining the predictive value of these biomarkers to distinguish FGD in quiescent IBD from a flare of IBD are currently not available.

Strikingly, the most recent technical reviews on diagnosis and management of IBD do not contain
explicit guidelines on the early detection of flares and their differentiation from IBS in IBD in remission, which are therefore eagerly awaited (70,71). Likewise, guidelines on the treatment of IBS in these patients are not available to date.

**CONCLUSION**

Inflammation is undoubtedly a powerful mediator of neuromuscular intestinal function. Inflammation-associated motility and sensitivity disturbances often survive the inflammatory episode, resulting in motility and sensitivity disturbances during remission. Inflammation at one site in the gut can lead to altered neuromuscular behavior at a distant site, suggesting perturbation of gastrointestinal reflexes. To date, mechanistic research on altered neurogastroenterology in patients with IBD remains largely anecdotal, although the impact of functional gut symptoms in these patients contributes to a large degree to IBD-related morbidity quality of life. As a consequence, therapeutic guidelines are absent in current literature and have to be extrapolated from measures taken in FGD in general. This emphasizes the need for a better documentation of the epidemiology and nature of FGD as they occur in patients with IBD during inflammatory episodes and remission.

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**References**


