Irritable bowel syndrome – a microbial perspective

Irritable bowel syndrome is a commonly occurring symptom complex of unknown cause. The condition is characterised by gastrointestinal problems, but is often accompanied by functional disorders in several organ systems. Disruption of the intestinal flora may be a causal factor, and this possibility should be further researched, not least as a basis for treatment.

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Irritable bowel syndrome is the most common functional gastrointestinal disorder and occurs in approximately 10 % of the population (1). The condition is characterised by pain, flatulence and disturbances in bowel movements. It was first described in a scientific journal in 1818 (2). The diagnosis is based on a combination of exclusion and inclusion criteria: organic diseases must be ruled out through adequate investigation (3), and internationally accepted symptom criteria have been drawn up which must be fulfilled in order to make the diagnosis (Box 1) (4).

The cause of irritable bowel syndrome is unknown, but since the condition was discussed in the Journal of the Norwegian Medical Association in 2002 (5), there has been a significant development in how its pathophysiology is viewed (6). In this article we will point to possible microbial mechanisms behind the symptoms.

A strategic position

The pathophysiology of irritable bowel syndrome is obviously complex, but there has long been a suspicion that abberations in one or more of the control systems of the gastrointestinal tract are involved in the development of symptoms. One of the most widespread explanations is a disruption to the interaction between the brain and the intestine (7).

Already in the 1800s the American military doctor William Beaumont (1785–1853) described how mood affected the digestion of the Canadian fur-trapper Alexis St. Martin (1794–1880), who had developed a gastrocutaneous fistula following a gunshot wound to his stomach (8).

Modern stress research has since discovered a number of signal pathways from the central nervous system to the gastrointestinal tract, both neural (the autonomic nervous system) and humoral (the hypothalamic-pituitary-adrenal axis). There is little doubt that activity in this brain-gut axis affects the behaviour of the intestine. The gastrointestinal tract is, however, largely autonomous thanks to extensive indigenous control systems: the enteric nervous system, the enteroendocrine system and the intestinal immune system. These components interact with one another and transmit information to the brain as nerve impulses, hormones and cytokines. Signals from the intestine thereby affect the brain's function, perhaps especially the activity of the limbic system (9), but we currently know little about the consequences of this.

The intestinal flora is in close contact with the control systems of the gastric wall, and this position enables a microbial effect on the host, including the central nervous system (10). From such a perspective, disruptions to the intestinal flora can be thought to explain a number of symptoms, both intestinal and extraintestinal. But do we have evidence to support the claim that microbial mechanisms are involved in the pathophysiology of irritable bowel syndrome?

In the following we will seek to elucidate this question by highlighting two crucial clinical points: that the symptoms can occur after infections of the gastrointestinal tract and that they are often exacerbated by the intake of certain foods.

Post-infectious problems

The recognition that irritable bowel syndrome may occur following infections is relatively new, although the phenomenon was described as far back as the 1950s (11). Long-term gastrointestinal problems may develop after viral, bacterial and parasitic forms of gastroenteritis (12). This so-called post-infectious subgroup of irritable bowel syndrome constitutes an estimated 10 % of the total number of cases (13). From a research point of view this is an attractive entity for study because the infection may be regarded as a kind of intervention in a natural experiment.

Post-infectious irritable bowel syndrome appears to be a clearly microbial condition, but the mechanisms behind the symptoms are unknown. Hitherto the research has largely focused on immunological factors, and a number of aberrations have been described in cell numbers and cytokine levels in intestinal biopsies and blood tests from patients with long-term gastrointestinal problems following various infections (14). There have been far fewer efforts to study the importance of the intestinal flora. This ought to be studied, since infectious forms of gastroenteritis not only affect the host, but also the host's microbes (15, 16).

In 2004 there was a major outbreak of gastroenteritis in Bergen, which turned out to be caused by polluted drinking water, in which the parasite *Giardia lamblia* was detected. It is estimated that around 2 500 patients were treated for giardiasis (17). The parasite was detected in the faecal samples of 1 252 patients. Three years later these patients were asked to complete a questionnaire (18). Of the 817 who responded, 46.1 % reported symptoms consistent with irritable bowel syndrome, 46.1 % reported symptoms consistent with chronic fatigue and 28.6 % had symptoms consistent with both.

Five years later, those who reported chronic fatigue were offered a thorough cross-disciplinary assessment. Of the 53 who attended for this assessment, 22 were diagnosed with chronic fatigue syndrome (19). The possibility that an infection that essentially restricts itself to upper sections of the small intestine may trigger such severe systemic symptoms is a completely new aspect.

Immunological mechanisms may be involved, and Hausken and collaborators have recently described an increased number of CD20-positive cells in duodenal biopsies from patients who have suffered from *Giardia* infection (20). Interestingly, this is the same cell population that is inhibited

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by rituximab, an antibody that may have positive effects in the treatment of chronic fatigue syndrome (21). Disruption of the intestinal flora is another possible explanation (22).

Fermentative dyspepsia revisited

A number of studies have investigated the composition of the intestinal flora using advanced molecular biological methods, and this is consistently thought to be altered in patients with irritable bowel syndrome compared with healthy persons (23). However, the findings are relatively subtle and disappointingly inconsistent, and it is unclear whether the changes detected are primary or secondary to disruption of the intestinal function. In any case, from a pathophysiological perspective such studies of the structure of the intestinal flora provide relatively limited information – it is far more important to investigate what the microbes do than who they are.

The main function of the intestinal flora is to break down nutrients which the host is unable to digest itself (24). Food substances that are poorly absorbed in the small intestine, primarily low-digestible carbohydrates, continue to the colon, where they undergo microbial fermentation. Intriguingly, it is precisely this type of food that often gives rise to symptoms in patients with irritable bowel syndrome (25). This hypersensitivity to food has long been neglected, but is now being taken seriously, exemplified by the fact that the renowned *American Journal of Gastroenterology* recently dedicated an entire issue to a review of the disorder (26).

Intake of food with a high FODMAP content (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) appears to play a central role in the development of symptoms (27). The Norwegian Directorate of Health now recommends that people with irritable bowel syndrome reduce their intake of these types of carbohydrates, which are found in large quantities in, for example, apples, fruit juice, wheat, broccoli, beans, milk and honey (28).

Interestingly, similar advice was given in the early 1900s in the treatment of fermentative dyspepsia (29). This diagnosis is no longer used, but it is worth noting that this old designation for irritable bowel syndrome expresses an essential aspect of the condition's pathophysiology, namely that fermentation processes seem to be involved. We still know little about why fermentation provokes symptoms in people with irritable bowel syndrome (30), but we suspect that microbial metabolites may play a significant role (31). Perhaps this can explain both the gastrointestinal problems and the associated health symptoms (32)?

Final comments

Microbial mechanisms appear, therefore, to be involved in the pathophysiology of irritable bowel syndrome. Until now, this has mainly been investigated using descriptive studies of the composition of the intestinal flora and testing of different types of antibiotics and probiotics (33). We must take on board that intestinal flora is an active metabolic organ and place much greater emphasis on studying the functions of the microbes.

Attempts to change the intestinal flora with antibiotics and probiotics are an interesting therapeutic principle for irritable bowel syndrome, but we do not yet have a full picture of their mechanisms of action and long-term effects, and this type of therapy can sometimes have unfavourable effects (34, 35).

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BOX 1

Diagnosis of irritable bowel syndrome according to the Rome III criteria (4). The patient must have suffered from recurrent abdominal pain or discomfort for more than six months. In addition the symptoms must have been present for at least three days per month for three months. At the same time at least two of the following factors must be present:

Symptoms improve with defaecation

Onset of symptoms associated with a change in frequency of stool

Onset of symptoms associated with a change in consistency of stool

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References

1. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012; 10: 712–21, e4.
2. Powell R. On certain painful afflictions of the intestinal canal. Med Trans Royal Coll Phys 1818; 6: 106–17.
3. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. Am J Gastroenterol 2002; 97: 2812–9.
4. Longstreth GF, Thompson WG, Chey WD et al. Functional bowel disorders. Gastroenterology 2006; 130: 1480–91.
5. Blomhoff S, Diseth TH, Jacobsen MB et al. Irritabel tarm-syndrom multifaktoriell lidelse hos barn og voksne. Tidsskr Nor Lægeforen 2002; 122: 1213–7.
6. Camilleri M. Peripheral mechanisms in irritable bowel syndrome. N Engl J Med 2012; 367: 1626–35.
7. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. Annu Rev Med 2011; 62: 381–96.
8. Wolf S. The psyche and the stomach. A historical vignette. Gastroenterology 1981; 80: 605–14.
9. Berntson GG, Sarter M, Cacioppo JT. Ascending visceral regulation of cortical affective information processing. Eur J Neurosci 2003; 18: 2103–9.
10. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012; 13: 701–12.
11. Stewart GT. Post-dysenteric colitis. BMJ 1950; 1: 405–9.
12. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. Gastroenterology 2009; 136: 1979–88.
13. Longstreth GF, Hawkey CJ, Mayer EA et al. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther 2001; 15: 959–64.
14. Öhman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat Rev Gastroenterol Hepatol 2010; 7: 163–73.
15. Fujita K, Kaku M, Yanagase Y et al. Physicochemical characteristics and flora of diarrhoeal and recovery faeces in children with acute gastroenteritis in Kenya. Ann Trop Paediatr 1990; 10: 339–45.
16. Barman M, Unold D, Shifley K et al. Enteric salmonellosis disrupts the microbial ecology of the murine gastrointestinal tract. Infect Immun 2008; 76: 907–15.
17. Nygård K, Schimmer B, Søbstad O et al. A large community outbreak of waterborne giardiasis-delayed detection in a non-endemic urban area. BMC Public Health 2006; 6: 141.
18. Wensaas KA, Langeland N, Hanevik K et al. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. Gut 2012; 61: 214–9.
19. Mørch K, Hanevik K, Rivenes AC et al. Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. BMC Gastroenterol 2013; 13: 28.
20. Hausken T, Dizdar V, Hanevik K et al. Duodenal mucosal lymphocyte subgroups in patients with persisting abdominal symptoms after Giardia lamblia infection. Abstrakt. Neurogastroenterol Motil 2012; 24 (suppl 2): 172.
21. Fluge O, Bruland O, Risa K et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS ONE 2011; 6: e26358.
22. Frémont M, Coomans D, Massart S et al. High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. Anaerobe 2013; 22: 50–6.
23. Salonen A, de Vos WM, Palva A. Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. Microbiology 2010; 156: 3205–15.
24. Valeur J, Berstad A. Hvorfor har vi tykktarm? Tidsskr Nor Legeforen 2008; 128: 1298–300.
25. Shepherd SJ, Parker FC, Muir JG et al. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Clin Gastroenterol Hepatol 2008; 6: 765–71.
26. Chey WD. The role of food in the functional gastrointestinal disorders: introduction to a manuscript series. Am J Gastroenterol 2013; 108: 694–7.
27. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. J Gastroenterol Hepatol 2010; 25: 252–8.
28. Kosthåndboken. Veileder i ernæringsarbeid i helse- og omsorgstjenesten. Oslo: Helsedirektoratet, 2012: 189–90.
29. Svartz N. Colitis fermentiva. Nordisk Lærebog i Intern Medicin. Bd. 2. København: Gyldendalske Boghandel – Nordisk Forlag, 1945.
30. Valeur J, Morken MH, Norin E et al. Carbohydrate intolerance in patients with self-reported food hypersensitivity: comparison of lactulose and glucose. Scand J Gastroenterol 2009; 44: 1416–23.
31. Campbell AK, Matthews SB, Vassel N et al. Bacterial metabolic 'toxins': a new mechanism for lactose and food intolerance, and irritable bowel syndrome. Toxicology 2010; 278: 268–76.
32. Berstad A, Undseth R, Lind R et al. Functional bowel symptoms, fibromyalgia and fatigue: a food-induced triad? Scand J Gastroenterol 2012; 47: 914–9.
33. Bonfrate L, Tack J, Grattagliano I et al. Microbiota in health and irritable bowel syndrome: current knowledge, perspectives and therapeutic options. Scand J Gastroenterol 2013; 48: 995–1009.
34. Maxwell PR, Rink E, Kumar D et al. Antibiotics increase functional abdominal symptoms. Am J Gastroenterol 2002; 97: 104–8.
35. Ligaarden SC, Axelsson L, Naterstad K et al. A candidate probiotic with unfavourable effects in subjects with irritable bowel syndrome: a randomised controlled trial. BMC Gastroenterol 2010; 10: 16.

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