Microbiota and irritable bowel syndrome

Flore et syndrome de l’intestin irritable

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Summary  Irritable bowel syndrome (IBS) is a multifactorial disease during which the pathophysiological role of the gut microbiota has been recently highlighted. In almost 20% of the patients, IBS is clearly a post-infectious IBS as a consequence of an acute bacterial gastroenteritis. Some papers have reported an abnormal colonic fermentation in IBS patients that could explain symptoms such as bloating and be one of the factors triggering visceral hypersensitivity. More recently, significant differences in the composition of both the luminal and mucosa-associated microbiota have been reported between both IBS patients and healthy controls and IBS subgroups while some arguments exist for a small intestinal overgrowth in a subset of IBS patients. All these arguments for a deleterious role of the gut microbiota lead to the actual discuss to consider new therapeutic options, including mainly pre- and probiotics and maybe antibiotics.

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Introduction

Irritable bowel syndrome (IBS) is the most common functional intestinal disorder and affects primarily women (sex ratio 2:1). It is characterised by chronic abdominal pain or discomfort without distinct anatomical anomaly and is associated with bowel transit disturbances (constipation, diarrhea or both) which are more pronounced during the painful episodes. On the basis of current definition criteria, the prevalence of IBS in the general population is around 10 to 12% [1]. Although not life-threatening, IBS significantly and chronically alters the quality of life of affected patients and requires more continuous care since traditional therapeutic options (antispasmodics, clay preparations, low-dose antidepressants) are not consistently effective [2]. For these reasons, it has become a genuine public health concern that requires a solution. Some recent progress has been made in understanding the pathophysiology of symptoms, through emphasis on the potential role of the microbiota and thus the subsequent opening of new therapeutic options.

Pathophysiology: the role of microbiota is increasingly emphasised

IBS is a multifactorial disease. The focus has successively been placed on the contributing role of gastrointestinal motility disorders, visceral hypersensitivity, disturbances of the bidirectional neuro-immuno-hormonal pathways which connect the central nervous system to the enteric nervous system, and the role of a minimal “inflammatory” bowel state with gastrointestinal immune disturbances. Depending on the patients, these different factors are involved to varying degrees in the genesis of symptoms [3]. More recently, attention has been brought to the role of the intestinal ecosystem in bowel transit disorders (diarrhea, constipation or both) but also to the triggering and persistence of abdominal pain and the occurrence of local proinflammatory cytokine production without mucosal lesions (Fig. 1).

Arguments favouring intestinal microbiota involvement

There are several arguments that support this role: a) intestinal bacteria influence the gastrointestinal physiology; b) IBS appears in some patients after an episode of acute gastroenteritis (post-infectious irritable bowel syndrome or PI-IBS); and c) qualitative and quantitative differences in the composition of the microbiota of the large and small intestines have been observed between IBS patients and control subjects.

Intestinal microbiota have an effect on gastrointestinal sensitivity and motility

In animals that are genetically lacking in microbiota, several gastrointestinal anomalies have been demonstrated: gastroparesis, significantly delayed small intestine transit time and large caecal distension [4]. The reconstitution of microbiota in these animals was associated with the appearance of organised small bowel motility including the occurrence of phase III migrating motor complexes spreading as far as the ileum. It also caused increased expression of enzymes involved in the synthesis of neuromodulators (such as gamma-aminobutyric acid) and the stimulation of specific muscle protein synthesis. These effects could be the result of catabolic activity that the microbiota (mainly from the colon) exerts on many exogenous or endogenous substrates [4]. The products of this colonic fermentation [gas (H2 and/or CH4) and short-chain fatty acids] also modulate the gastrointestinal motility, especially in the ileocolic region, affect the functioning of epithelial and intestinal immune cells [4] and can influence gastrointestinal sensitivity, with the possible occurrence of hypersensitivity [5].

Excessive colonic fermentation with IBS

One of the roles of colonic microbiota is the luminal transformation of carbohydrates. This fermentation leads to the production of gas, primarily hydrogen and methane. During a standard diet, the production of hydrogen is excessive with IBS while the volume of gas products is normal. This fact was demonstrated during a normal diet through 24-hour measurement of this gas production using a whole-body

Peripheral Mechanisms

Dysmotility

Sensitization of sensory endings

Low grade Inflammation

Altered permeability

Microbiota

Figure 1 Pathophysiology of irritable bowel syndrome: a dysfunction of the brain gut-axis.
calorimeter [6]. The nycthemeral production of hydrogen was two times greater with IBS than in a control population that had a much higher rate of this gas production after a meal. The authors of the work also demonstrated a correlation between the occurrence of symptoms and the rate of hydrogen production [6]. With a diet excluding grains other than rice, as well as milk products, hydrogen production was significantly reduced in the same IBS subjects but not in the controls. This lowered production resulted in improvement of symptoms that were usually triggered by food intake [6]. Another study in which the production of hydrogen and gas was reduced by direct action on the microbiota through the administration of metronidazole (400 mg, 3 times per day for 2 weeks) obtained equivalent results and demonstrated the same correlation between the reduction of fermentation processes and symptomatic improvement [7] (Fig. 2).

Some IBS cases after an initial acute gastrointestinal infection

The existence of post-infectious IBS (PI-IBS) is now accepted. Once suggested through anecdotal observations in the 1960’s and 1970’s, this hypothesis was confirmed through several subsequent epidemiological studies [8, 9]. PI-IBS makes up 15% to 20% of IBS cases and can occur following a bacterial (salmonellosis, shigellosis, campylobacter gastroenteritis) as well as parasitic (Giardia intestinalis) infection [10]. The relative risk of developing IBS is increased five-fold following a gastrointestinal infection, with several factors contributing to this risk. The most important risk factor is the duration of the initial infection. Longer is the duration, higher is the risk of PI-IBS. The probability of PI-IBS is increased 11-fold when the initial infection lasts more than 3 weeks, whereas it does not differ from that of a control population after a brief infection (less than 7 days) [11]. The other risk factors of PI-IBS are host-related: young age at the time of infection, as well as the existence of an underlying anxious and/or depressive state [11]. PI-IBS results mainly from the persistence of a local “low grade inflammatory state” after the acute infection. By analysing the production of interleukin 18, a pro-inflammatory cytokine, on mucosal biopsies, the Nottingham team showed that the patients who developed PI-IBS were those that continued to have high levels of this cytokine three months after the infection [12]. The co-existence of an inflammatory infiltrate however has not been consistently reported, although it was observed in the rectum [13].

The gastrointestinal ecosystem may be quantitatively and/or qualitatively abnormal with IBS

Two types of microbiota anomalies have been described in cases of IBS.

Quantitative modifications

Based on abnormal results of a lactulose breath test that measures the production of hydrogen after lactulose loading, some authors have raised the hypothesis of quantitative disturbances of the microbiota with the presence of bacterial overgrowth in the small intestine [14]. This chronic bacterial colonisation of the small intestine leads to an increased hydrogen and methane production since the carbohydrate fermentation zone is no longer limited to the colon but also occurs in the ileum and even the distal jejunum. This overgrowth promotes the occurrence of intestinal inflammation.

Figure 2 The reduction of gas production improves irritable bowel syndrome symptoms (Dear KL et al. [7])
and triggers intestinal motor disturbances. The predominant
gas which is produced influences the symptomatic profile of
patients, with an increased production of methane parti-
cularly common in patients with constipation-predominant
IBS and a correlation between the quantity of methane
produced and the severity of slowed bowel transit [15]. The
theory of endoluminal bacterial overgrowth, which has mainly
been formulated by the team of Pimentel et al. in Los Angeles,
was supported by the demonstration of a significant symptomatic
improvement after a ten-day treatment with neomycin
[16] or rifaximine [17]. Reduced abdominal discomfort and
bowel transit disturbances occurred mainly in patients with
a high level of methane production before the antibiotic
treatment. This theory of endoluminal bacterial overgrowth
is still being actively debated. In the work by Pimentel et al.,
the prevalence of abnormal respiratory tests in a population
of 202 patients with IBS who underwent routine testing was
in fact 78%. This surprising high prevalence contrasts with
that which was reported in other studies which showed
either a prevalence that did not differ from that calculated
in a control population of asymptomatic subjects and close
to 4% [18], or a only slightly higher prevalence, with about
30% abnormal tests [19]. The discussion is essentially foun-
ded on the diagnostic performances (sensitivity, specificity,
negative and positive predictive values) of a hydrogen res-
piratory test based on the ingestion of glucose or lactulose
for affirming the existence of bacterial overgrowth in the
small intestine. The discussion especially centres on the
selection of criteria on which to base abnormal test results
[20]. Nevertheless, a recent meta-analysis, which took
into account the heterogeneity of the published studies,
concluded that the probability of endoluminal bacterial
overgrowth is about three times greater than that of a
control population [20]. It seems reasonable to conclude
that endoluminal microbial overgrowth is probable in some
patients, especially in those with small intestine motility
disturbances [18], and contributes to the abdominal bloating
which IBS patients complain of.

Modifications in the distribution of bacterial populations

In the absence of any chronic bacterial colonisation of the
small intestine in IBS, some data report modifications in the
composition of the endoluminal microbiota as well as in the
thin layer lining the mucosa. The first studies, based on the
culture of faecal bacterial microbiota, reported a decrease
in *Clostridium*, *lactobacilli* and *bifidobacteria* and an increase of
tenterobacteria, *coli* and bacteroides [21]. Methodologically
however, these results were not completely satisfactory
since some bacterial strains of human microbiota cannot
be cultivated. A Finnish study avoided this bias during the
comparison of the faecal bacterial microbiota found in
patients with IBS according the Rome II criteria who had
not taken antibiotics and healthy controls. In this study,
the characterisation of the bacteria was made by the
sequencing of the ribosomal 16S fraction [22]. This study
led to two types of very important results: a) it confirmed
that the microbiota were different between IBS patients and
healthy controls, with a distinct reduction of lactobacilli
and *Collinsella* in the first group; and b) it was the first
to identify notable differences in the composition of the
faecal microbiota between the IBS subgroups, with a greater
proportion of bacteroides and *Allisonella* in patients with
alternating diarrhoea-constipation, and a lower number of
bifidobacteria in the subgroup with diarrhoea only [22].

A single study is currently available which provides
information on the mucosal microbiota with the analysis of
intestinal mucosa biopsies. This study led to similar results
to the studies based on an analysis of faecal microbiota:
the mucosal microbiota was not the same between healthy
controls and IBS patients. The latter group showed an
increase in anaerobes, *Escherichia coli* and bacteroides
[23].

How can the microbiota data be integrated in the pathophysiology of IBS?

The differences in microbiota composition are important
to consider, especially as there are increasingly convincing
arguments in favour of mucous immune activation with
increased production of pro-inflammatory cytokines with IBS.
The anti-inflammatory effects of some strains of lactobacilli
and bifidobacteria have been demonstrated [4]. Reduction
of certain bacterial colonies could be a factor leading to
the activation of the host’s immune system, especially
after an initial gastrointestinal infection. Furthermore, the
different bacterial colonies do not have the same metabolic
properties. For example, the bifidobacteria mainly trans-
form oligosaccharides, whereas the bacteroides have both
proteolytic and saccharolytic activity [4]. The differences
in the intestinal gas production as highlighted by the study
by King et al. could be explained by these qualitative diffe-
rences in the microbiota. Moreover, some but not all studies
show that an increased production of gas or butyrate could
induce rectal or colonic hypersensitivity to distension [5,
24, 25]. In parallel, the development of bacterial colonies
with higher gas and fatty acid production, and which are
therefore more likely to deconjugate the biliary acids, is a
factor which could alter the transfer of water and elec-
trolytes, the sensitivity and motility of the colon and promote
the occurrence of diarrhoea.

Conclusions

In IBS, a multifactorial disease, we have now an increasing
number of arguments supporting the possibility that diffe-
rences in the composition and metabolic activities of the
intestinal microbiota compared to a control population can
play a significant role in the pathophysiology of the disease.
These arguments open the way to new therapeutic options
through logical attempts at influencing the microbiota by
the administration of probiotics and/or prebiotics [26], and
perhaps antibiotics [27]. The results of probiotics for this
indication are encouraging [28].

Conflicts of interests

None
References