MICROSCOPIC COLITIS AND SMALL INTESTINAL BACTERIAL OVERGROWTH – DIAGNOSIS BEHIND THE IRRITABLE BOWEL SYNDROME?

Adriana Stoicescu¹, M. Andrei¹, G. Becheanu², M. Stoicescu³, T. Nicolaie¹, M. Diculescu²
Emergency University Hospital Elias, Bucharest
1. Gastroenterology, Hepatology and Digestive Endoscopy Clinic, Fundeni Clinical Institute, Bucharest
2. Centre of Gastroenterology and Hepatology,
3. „M. S. Curie” Children’s Emergency Hospital, Bucharest

MICROSCOPIC COLITIS AND SMALL INTESTINAL BACTERIAL OVERGROWTH – DIAGNOSIS BEHIND THE IRRITABLE BOWEL SYNDROME? (Abstract): Some patients previously diagnosed with irritable bowel syndrome (IBS) may develop microscopic colitis or small intestinal bacterial overgrowth (SIBO). **Aim:** To estimate the prevalence of microscopic colitis and SIBO in patients with IBS, to evaluate the symptoms and the efficacy of treatment. **Material and methods:** We examined patients with IBS admitted in our clinic during a three-year period. We identified patients with microscopic colitis by performing total colonoscopy with multiple biopsies from normal intestinal mucosa and those with SIBO by performing a H₂-breath test with glucose. We compared the symptoms and the effectiveness of the treatment. **Results:** Out of the 132 patients initially diagnosed with IBS 3% (n=4) had microscopic colitis and 43.9% (n=58) had SIBO. Diarrhea was the main symptom in patients with microscopic colitis and SIBO (p=0.041), while abdominal pain, abdominal bloating and flatulence were prominent in IBS patients (p=0.042; p=0.039; p=0.048). Specific treatment with rifaximin in SIBO patients negativated H₂-breath test in 70.9% cases. **Conclusions:** Patients suspected to have irritable bowel syndrome should be evaluated for microscopic colitis and SIBO. The proper diagnosis and the specific treatment may cure some difficult cases of the so called “irritable bowel syndrome”. **Key words:** irritable bowel syndrome, microscopic colitis, collagenous colitis, lymphocytic colitis, small intestinal bacterial overgrowth.

With prevalence between 2.5 and 22% worldwide, irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder with heterogenous clinical manifestations and no pathognomonic features. Differentiation of IBS from other diseases may be sometimes difficult, especially when colonoscopy looks totally normal (1, 2, 3).

Microscopic colitis (MC) became a frequent diagnosis in the last years. The symptoms are similar to the IBS ones. The mucosa appears normal during colonoscopy, but multiple biopsies are required for a diagnosis that depends on well-defined histological criteria (4, 5, 6, 7, 8).

Another disease similar in clinical manifestations with IBS is small intestinal bacterial overgrowth (SIBO). It is characterized by an increased number (≥105 CFU/mL) and/or abnormal type of bacteria in the small
Microscopic colitis and small intestinal bacterial overgrowth

bowel. The gold standard for diagnosis is the microbial culture of jejunal aspirates, but because of its invasivity H2-breath tests are currently the most important diagnostic methods in SIBO, even if their accuracy is not so high (9, 10, 11, 12).

Our study is therefore aimed to estimate the prevalence of microscopic colitis and SIBO in patients diagnosed with IBS according to Rome III criteria and to compare clinical and epidemiological features of the patients in the three groups. We have also evaluated the effectiveness of treatment with rifaximin in patients diagnosed with SIBO.

MATERIAL AND METHODS

We included in our prospective study patients with a prior diagnosis of IBS, admitted in our clinic between April 2007 and April 2010. The diagnosis of IBS was confirmed on the basis of Rome III criteria and colonoscopy was performed. Prior to inclusion in the study all participants signed an informed consent form. Our study had the approval of Elias Hospital Ethics Committee.

Based on abnormal laboratory tests and colonoscopy some patients were excluded from the study. We insisted on the history of drug consumption and the presence of an acute episode of gastroenteritis before the onset of IBS-related symptoms. Clinical evaluation form registered data about the prominent symptoms, time between the onset of symptoms and the diagnosis of IBS, MC and SIBO and the treatment applied.

During colonoscopy at least four biopsies of normal mucosa from different regions of the colon were taken. Minimal macroscopic lesions (erythema, edema or superficial ulcers of mucosa) were noticed. Characteristic histopathological changes for collagenous colitis were: subepithelial collagenous band thickening > 10 μm, increased number of inflammatory cells in lamina propria, increased intraepithelial lymphocytes and possible surface epithelial damage. Lymphocytic colitis was defined by > 20 intraepithelial lymphocytes/100 epithelial cells and an increased number of inflammatory cells in the lamina propria, associated with normal collagen band. Superficial epithelial injuries were also identified.

All patients in the study group underwent glucose breath test in order to detect SIBO. We measured H2 in expired air before and after ingestion of 50 g of glucose dissolved in 250 ml water. Measurements were performed every 15 minutes for 120 minutes; the test was positive if one value of expired H2 exceeded 10-12 ppm over baseline. In patients with positive glucose breath test rifaximin was administered at the daily dose of 1200 mg for 7 days and the test was repeated after two weeks. Simultaneously with the second test patients completed a new clinical form.

We noticed the following: the criteria for MC and/or SIBO in patients with IBS, the demographic features of the patients, the main clinical manifestations, the possible association of autoimmune diseases and drugs in microscopic colitis patients, the period of time between the onset of symptoms and the diagnosis of IBS, MC and SIBO and the outcome after treatment.

Demographic and clinical characteristics of patients in the study group were compared statistically by Student-t test for quantitative variables and χ² test for qualitative variables. Statistical hypothesis testing was performed by calculating the value of p (p < 0.05 considered statistically significant) and 95% confidence interval. Data were statistically analyzed using SPPS.
version 17.0 software.

RESULTS
Figure 1 summarizes the general methodology and the results of our study.
We confirmed the diagnosis of IBS based on Rome III criteria in 132 patients. Depending on their predominant transit disorder they were classified into three types of IBS: with diarrhea (39.4%), with constipation (23.5%) and with mixed bowel changes (37.1%).

The average age of patients in our study group was 46.2 ± 15.2 years, and there was a predominance of women (59.1%). In 12 patients (9.1%) we identified a history of an acute gastroenteritis. The most frequent symptoms were transit disorders (diarrhea or alternating diarrhea/constipation), bloating, flatulence and abdominal pain. Blood tests (including thyroidian hormones, antinuclear antibodies and rheumatoid factor), abdominal ultrasound and microbiological stool examination were normal in all patients. Fecal calprotectin test was positive in 15 cases (11.4%).

All 132 patients underwent lower gastrointestinal endoscopy, which detected minimal colonic mucosal changes in 10 patients (7.6%). Following detailed histopathological examination of normal mucosa biopsies, microscopic colitis was found in only four patients. The main clinical and biological characteristics of patients with

Fig. 1. Methodology and study results
MC are listed in table I.

Based on positive results on breath test we confirmed the presence of SIBO in 58 patients (43.9%): 67.2% women and 32.8% men. The mean age was 42.5 ± 14.8 years. The most common symptoms were diarrhea and bloating, as well as in patients with IBS. Positive fecal calprotectin test was observed in only 13.8% patients.

56 patients with SIBO received rifaximin at the daily dose of 1200 mg for 7 days. Only 31 patients (55.3%) came to repeat the test after 2 weeks. In retested patients, negativity was achieved in 70.9%. For the 9 patients with positive second test a new cycle of rifaximin was prescribed and 3 patients had a negative breath test after two weeks. There were no side effects during treatment and obtaining negative breath test was followed by partial or total remission of symptoms in all patients.

**TABLE I**

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>MC type</th>
<th>Smoker</th>
<th>Celiac disease</th>
<th>NSAIDs</th>
<th>PPI</th>
<th>Diarrhea/nocturnal</th>
<th>Weight loss</th>
<th>Period of symptoms</th>
<th>Calprotectin</th>
<th>Normal mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>46/F</td>
<td>LC</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes/no</td>
<td>No</td>
<td>2 years</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>58/F</td>
<td>CC</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes/yes</td>
<td>No</td>
<td>6 years</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>65/M</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes/yes</td>
<td>Yes</td>
<td>5 months</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>72/F</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes/yes</td>
<td>Yes</td>
<td>7 weeks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Correlating the type of the disease with symptoms we found that diarrhea and nocturnal diarrhea were common manifestations in patients with SIBO (p=0.041) and abdominal pain was more frequent in patients with IBS (p=0.042). The following were also more common in patients with IBS: abdominal bloating (p=0.039) and flatulence (p=0.048). For other symptoms we obtained no statistically significant values (fig. 2).

**Fig. 2.** Comparison of symptoms in patients with IBS and SIBO
DISCUSSION

An increasing number of papers in the literature claim that a diagnosis of IBS could hide some other entities. After successful exclusion of the most frequent causes of chronic diarrhea or persistent constipation a number of rarely identified diseases can mimic IBS. Two of them have drawn our attention: microscopic colitis and SIBO.

Microscopic colitis has become a more frequent diagnosis in the last years due to increasing awareness of physicians as well as to a greater accuracy of diagnostic methods. A study performed in Sweden on 1018 patients identified microscopic colitis in 10% of the patients who underwent colonoscopy for chronic watery non-bloody diarrhea, the percentage increasing to 20% when only patients above the age of 70 were considered (7). Another study on 30 patients previously diagnosed as having IBS reported an incidence of lymphocytic colitis of 23.5%, while other authors found among diarrhea-IBS patients an incidence for collagenic colitis of 7.2% and for lymphocytic colitis of only 2.2% (13, 14). In our group the frequency of MC was lower: 3% of the total of IBS patients and 7.7% of the diarrhea-IBS. Due to the small number of microscopic colitis, statistical interpretation was not possible, but the symptoms were similar to those described by other studies (14, 15).

An association between MC and the use of specific drugs was reported, especially NSAIDs (up to 34%), proton pump inhibitors (Lansoprazole) and ticlopidine (14, 15, 16). Of our four patients with MC, one was treated with NSAIDs and one with Lansoprazole before the onset of diarrhea, which led us to consider these drugs as causative. The association between MC and other autoimmune diseases is seen up to 40% of cases, the most frequent being rheumatoid arthritis, celiac disease, tiroiditis and diabetes. We identified in our group a single case of celiac disease in a patient with lymphocitic colitis.

Budesonide appears to be the optimal drug choice for treating microscopic colitis nowadays. Despite this fact, only one patient in our study had to be treated with budesonide, the other three improved on symptomatic treatment (loperamide).

SIBO can be identified in 45-50% of IBS patients, partly explaining the symptoms (12, 17, 18, 19). Based on glucose breath tests we were able to diagnose SIBO in 43.9% of IBS patients. The major part (65.5%) was experiencing diarrhea, while fewer experienced chronic constipation (20.7%) or mixed transit disturbances (13.8%). The second frequent complain in our group of SIBO patients was bloating (56.9%), a symptom that most authors regard as the most specific sign of alterations in the intestinal flora (12).

One week of rifaximin 1200 mg/day has led to negative results of the glucose hydrogen breath test in 70.9% of cases. Our data confirm the results of other studies which showed a positive response between 59.4% and 82.6% for SIBO patients treated with rifaximin, with or without subsequent treatment with probiotics. Repeated courses of rifaximin in initial non-responders has led to a favourable outcome in 33.3% of cases, a better response than the ones obtained with ciprofloxacin, norfloxacin, amoxicillin - clavulanate, gentamicin, co-trimoxazole, polymyxins or tetracyclin (12, 18, 19).

Symptoms in IBS, MC and SIBO pa-
Microscopic colitis and small intestinal bacterial overgrowth

tients show some degree of overlap, but also a few significant differences. Most patients experiencing diarrhea (80.76%) and especially those with nocturnal diarrhea (78.57%) have been diagnosed with MC or SIBO. Abdominal pain, bloating and flatulence were described more frequently in patients with IBS and less in MC or SIBO patients. In what calprotectin is concerned, we found positive tests more frequently in MC and SIBO (80%) and only a smaller proportion in IBS patients.

CONCLUSIONS
We can conclude that, in order to correctly identify MC or SIBO, patients presenting as IBS should undergo an initial evaluation including colonoscopy with multiple level biopsies from normal-appearing mucosa and a glucose or lactulose hydrogen breath test. The symptoms of the three described conditions are very similar. Nocturnal diarrhea and a positive stool test for calprotectin can help differentiating MC and SIBO patients from those suffering from IBS, but their specificity is far from 100%. Specific management with budesonide in MC and with rifaximin in SIBO leads to significant clinical improvement and a favorable response in difficult to treat cases of „irritable bowel syndrome”.

REFERENCES
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EXTRACELLULAR MATRIX ADMINISTRATION AS A POTENTIAL THERAPEUTIC STRATEGY FOR PERIODONTAL LIGAMENT REGENERATION

The current strategies employed for the treatment of connective tissue disease include the application of stem cells, the use of functional molecules that can reorganize tissue integrity and cellular activities to recover connective tissue function. Approaches to the regeneration of periodontal tissue, which is the tooth-supporting connective tissue, have made some progress recently and provide a useful experimental model for the evaluation of future strategies to treat connective tissue diseases such as periodontal disease. The ultimate goal of periodontal tissue regeneration is to reconstruct the ligament structure that will sustain the required mechanical force to connect with mineralized tissues such as cementum and alveolar bone. The administration of extracellular matrix could be used as an additional therapeutic strategy to stem cell transplantation and cytokine administration in periodontal tissue regeneration therapy. Although various available tissue engineering technologies can now achieve periodontal tissue regeneration, extracellular matrix administration therapy is likely to play an essential future role in the development and regeneration of periodontal tissue and attenuate the signaling events that mediate tissue degradation. Hence, extracellular matrix administration could serve as a novel technology in periodontal tissue regeneration and also as a viable approach to alleviating connective tissue disorders such as Marfan's syndrome [Saito M, Tsuji T. Extracellular matrix administration as a potential therapeutic strategy for periodontal ligament regeneration. Expert Opin Biol Ther. 2012 Mar;12(3):299-309].

Gianina Iovan