

Four years Follow-up of Patients with Irritable Bowel Syndrome

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There is little data on the long term evolution of patients with irritable bowel syndrome (IBS) and of associated conditions. We therefore studied the evolution of IBS patients in a single tertiary center during a long interval of time.

Methods. We carried out a retrospective study based on the survey of patients records. We analyzed the records of symptoms, therapy, associated diseases, as consigned at follow-up visits for an interval of 4 years in average (2008-2011).

Results. A cohort of 114 patients with IBS diagnosed based on Rome III criteria were included (29 men and 85 women), age 19-85 years (mean age: 43.45 years). Urban patients were predominant. The main three symptoms were: abdominal pain, bowel disorders (constipation, diarrhea) and bloating. IBS - constipation (IBS - C) is associated with a favorable course of symptoms (increasing the number of stools, decrease intensity of abdominal pain and bloating) after treatment and IBS - diarrhea (IBS - D) is associated with variable symptoms after treatment ($p = 0.031$). Using trimebutin or mebeverin in association with other drugs for one month correlates with a favorable evolution of symptoms after treatment and monotherapy is associated with fluctuating symptoms ($p < 0.001$). Favorable symptoms are associated with the use of probiotics in combination, but not in monotherapy ($p < 0.001$). Favorable evolution of symptoms is also associated with the use of anxiolytics in combination. Persistence of symptoms after treatment was correlated with the presence or absence of depression. The absence of depression was correlated with a favorable evolution of symptoms ($p = 0.005$). IBS-C is associated at limit (marginal significance) with hemorrhoidal disease ($p = 0.56$). 33 patients (29%) – received monotherapy (trimebutin or mebeverin or probiotics); 81 patients (71%) – received combined therapy: (trimebutin or mebeverin or probiotics) + anxiolytics or proton pump inhibitors (PPI) or nonsteroidal anti-inflammatory (NSAI) or spasmolytics. The most common associated diseases observed in patients with IBS were: depression (27.19%), dyslipidemia (25.43%), hemorrhoidal disease (22.80%) and fibromyalgia (21%).

Conclusions. The highest response rate was obtained with trimebutin or mebeverin + anxiolytics + probiotics. The most frequent disease associated with IBS was depression. Other diseases with a high incidence: dyslipidemia, hemorrhoidal disease and fibromyalgia. Further studies are needed to analyze the link between IBS and some associated diseases.

Key words: IBS, symptoms, treatment, associated diseases.

Irritable bowel syndrome (IBS) is defined as an alteration of the intestinal transit associated with pain. It is a frequently found condition, affecting about 20% of the general population, mainly females [1]. IBS is defined as polymorphic symptoms (abdominal discomfort, bloating, intestinal cramps) associated with bowel disorders (diarrhea, constipation or alternating thereof) in the absence of any organic gastrointestinal modifications. The symptoms are troublesome and affect the quality of life and work capacity of patients who can increase the risk of occurrence of depression and social isolation [2, 3].

Management of patients with severe or persistent clinical manifestations is often a challenge for gastroenterologists [4].

In the literature, only a few studies which were aimed at follow-ups of long-term patients with IBS have been published. IBS has been reported to be associated with a wide variety of symptoms, psychological and physical distress affecting quality of life and increasing the use of resources in the health system [5, 6]. In this population, the fear of having severe gastrointestinal disease or other diseases is a common reason for which patients seek medical attention [7, 8]. Correct diagnosis of comorbidities is very important for accurate diagnosis and choice of the optimal treatment for this group of patients. Although IBS is not life threatening, excluding some serious diseases, such as various types of gastrointestinal cancer, represents a major clinical

challenge. Therefore, taking clinical decision is often difficult, considering that psychological factors, social and biological, all play a role, although the impact of each of these factors is probably different for some patients than others and may vary in time for the same person [9-12]. Therapies available today are aimed at the multifactorial etiology and include both pharmacological and non-pharmacological treatment, for example hypnotherapy and cognitive behavioral therapy [13, 14]. Some studies have shown that approximately 50% of patients with IBS in the primary care system, but also in hospitals, have at least one symptom or associated disease [15]. Hudson *et al.* have described comorbidities related to IBS such as fibromyalgia, some migraines, chronic fatigue syndrome, major depression and panic attacks [16]. Patients with one or more diseases associated with IBS tend to report more severe symptoms, more physical complaints and more disease-related absenteeism than patients without comorbid disorders [17, 18]. Psychosocial factors may also influence the medical staff seeking information in addition to IBS itself [19]. Anxiety and depression were reported to be more common in patients with IBS than in healthy control subjects. However, a causal relationship between IBS and psychosocial factors is still unknown [20].

AIM

The purpose of this study was to analyze the evolution of IBS symptoms in a cohort, during a longer interval of time. We also investigated the response to therapy and looked for the associated diseases among patients with IBS.

METHODS

PROTOCOL

We performed a retrospective longitudinal study using data from our Medical Database, from Second Medical Department, Cluj-Napoca. The information recorded includes demographics, medical diagnoses, referrals for consultants and hospitals, and a register of written prescriptions. The diagnosis (according to ROME III criteria) or indications for new courses of therapy were also registered. We identified all patients aged between 19 and 85 years

old, mean age 43.45 years, with a first time recorded diagnosis of IBS in 2007. Women who were pregnant at the time of recorded IBS diagnosis, as well as patients with cancer or alcohol-related diseases were excluded. A patient was defined to be newly diagnosed with IBS if, prior to the date on which IBS was first recorded, there were no signs of IBS or other gastrointestinal diseases such as peptic ulcer disease, GERD (gastroesophageal reflux disease), inflammatory bowel disease, ulcerative colitis, Crohn's disease, pancreatitis or cholecystitis. We collected recorded information on demographic characteristics and risk factors (smoking status, weight, height and alcohol consumption).

We recorded the prevalence of conditions that have been associated with IBS: depression, anxiety, migraine, headache, chronic fatigue syndrome, insomnia, asthenia, nausea, eructation, heart palpitations. We also recorded the prevalence of associated diseases: dyslipidemia, hemorrhoidal disease, fibromyalgia, coronary heart disease, diabetes, cholecystectomy, cholelithiasis, gastritis, osteoporosis, kidney stones, nodular goiter, spinal arthrosis, hypothyroidism and spinal discopathy. We followed up the group of IBS patients for 4 years.

Routine check-ups were initially performed at one month, thereafter at 6 month intervals. At every routine check-up the main symptoms were observed and evaluated: abdominal pain, bowel disorders, flatulence and bloating.

The treatment administered to these patients was directly related to symptom severity. Symptom severity was not assessed using a specific questionnaire, but based on individual perception of each patient, compared to the severity of symptoms from disease onset. During follow-ups, we recorded morbidity status, general practitioner visits, referrals and hospitalizations.

We also assessed drug treatment for IBS: Trimebutine 300 mg, Mebeverine 200 mg, probiotics (e.g. Linex, Biotics, Eubiotic), anxiolytics (e.g. Alprazolam 0.25 mg, Bromazepam 1.5 mg), PPI (e.g. Omeprazol 20 mg, Esomeprazol 20 mg, Pantoprazol 20 mg), NSAID (e.g. Ibuprofen 200 mg, Etoricoxib 120 mg, Naproxen 200 mg, Ketoprofen 200 mg), spasmolytics (e.g. Drotaverin 40 mg, Otilonium bromide 40 mg). Trimebutine, Mebeverine and probiotics were used as monotherapy, but also

in combination with the other drugs. The rest of the mentioned drugs were used in combination only, not as monotherapy. The treatment plan was individualized for each patient depending on the severity of symptoms and associated diseases. We registered all the investigations performed for the diagnosis. We analysed the distribution of patients characteristics, treatment patterns and symptom evolution according to the treatment plan.

STATISTICAL METHODS

We used SPSS version 22.0 for Windows. We analyzed symptoms over time, symptoms after treatment, visit frequency, evolution of symptoms according to IBS type and to medication regimen, IBS association with other diseases like depression, hemorrhoidal disease and other comorbidities using chi squared test. We compared means and significance of the results using t-test. A value of p less than 0.05 was considered to be significant. Correlations were calculated using Pearson test.

RESULTS

The following items were analyzed: symptom onset, associated diseases, origin (urban or rural), evolution and therapy for symptoms followed by patients.

The distribution of the patients by year (2008: 21 patients, 2009: 25 patients, 2010: 31 patients and 2011: 37 patients) shows a higher number of patients in the last 2 years of follow-up.

Concerning subtypes of IBS, most of the patients were with predominant constipation (Fig. 1).

Of the total 114 patients, 29 were men and 85 were women. In general, female patients diagnosed with IBS had more several diseases associated with IBS than males. Concerning the origin of patients, 37 were from rural areas and 77 from urban areas (Table I).

The main complaints: abdominal pain, bowel disorders, bloating and flatulence (Table II).

Of the 114 patients, 84% had insidious onset of symptoms with rare exacerbations which gradually increased in intensity and 16% had sudden onset of symptoms, with a relatively similar level of intensity (Fig. 2).

Regarding symptom evolution after treatment, 54% of the patients had favorable evolution, with a significant decrease in frequency of symptoms,

36% of the patients had fluctuating evolution with decreased severity of symptoms and 10% of the patients had no favorable evolution of symptoms after treatment (Fig. 3).

62% of patients visited a doctor for routine control or exacerbation of symptoms more than once a year, 36% of patients visited a doctor for routine control or exacerbation of symptoms 2-4 times per year and 2% of patients did not visit a physician since the first consultation (Fig. 4).

Of the total 114 patients, 33 (29%) received monotherapy with trimebutine, mebeverine or probiotics. 81 patients (71%) received combined therapy: (trimebutine or mebeverine or probiotics) + (anxiolytics, PPI, NSAID, spasmolytics). IBS - C and IBS C+D were associated with favorable evolution of symptoms after treatment and IBS with predominance of diarrhea was associated with different intensities of symptoms after treatment administrations ($p = 0.031$) (Table III).

The use of trimebutine or mebeverine in association with other drugs was correlated with improvement of symptoms after treatment ($p < 0.001$) and monotherapy was associated with fluctuating symptoms ($p < 0.001$) (Tables IV, V).

The favorable evolution of symptoms was associated with the use of probiotics in combination ($p < 0.001$), but not in monotherapy ($p < 0.001$) (Tables VI, VII).

Favorable evolution of symptoms was also associated with the use of anxiolytics in combination. The symptoms after treatment were correlated with the presence or absence of depression (Tables VIII, IX). Favorable evolution of symptoms after treatment was shown by patients who suffer from depression ($p = 0.005$).

The most common symptoms exhibited by patients with IBS were headache, migraine, anxiety and depression (Fig. 5).

The most common accompanying diseases observed in patients with IBS were: depression, dyslipidemia, hemorrhoidal disease and fibromyalgia (Table X).

Numerous other diseases were associated in patients with IBS. The most commonly found were: obesity (18 patients), high blood pressure (18 patients), colon polyps (16 patients), coronary heart disease (16 patients), diabetes (15 patients), cholecystectomy (14 patients), vesicular gallstones (12 patients), gastritis (12 patients), osteoporosis (12 patients), kidney stones (11 patients), nodular goiter (9 patients), spinal arthrosis (7 patients), hypothyroidism (6 patients), spinal discopathy (5 patients) (Fig. 6).

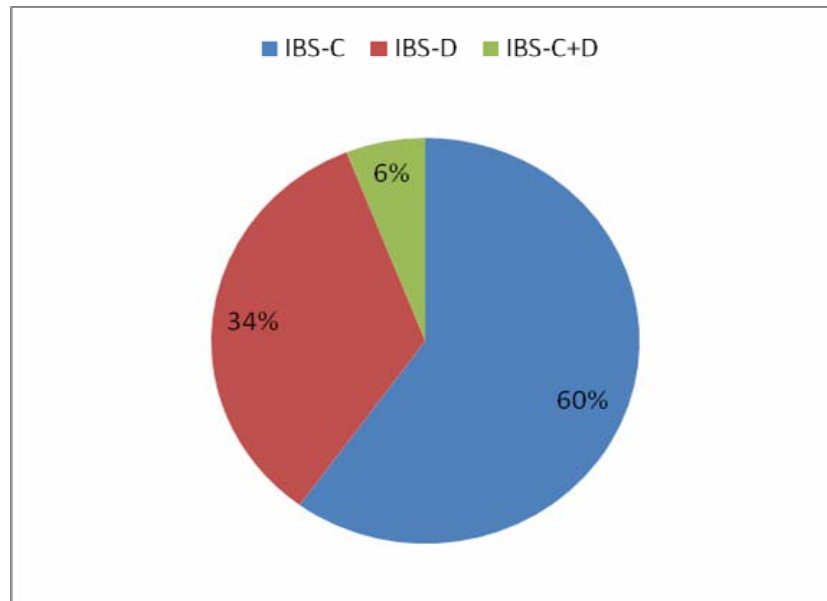


Figure 1. IBS subtypes

(Of the total of 114 patients, 60% of the patients were with predominant constipation, 34% with predominant diarrhea and 6% mixed).

Table I

Demographic data of IBS patients

IBS patients	Nr.	%
GENDER		
Male	29	25.43
Female	85	74.57
AGE		
18-30	34	29.82
31-50	63	55.26
51-85	17	14.91
RURAL		
Male	9	31.03
Female	26	30.58
URBAN		
Male	20	68.97
Female	59	69.42

Table II

Frequency values for each symptom

Frequency	Symptom %			
	Abdominal pain	Bowel disorders	Bloating	Flatulence
daily	20.17	34.21	18.4	27.57
at least 2-3 times/week	53.5	59.64	77.17	60.4
1-4 episodes/month	26.33	6.15	4.43	12.03

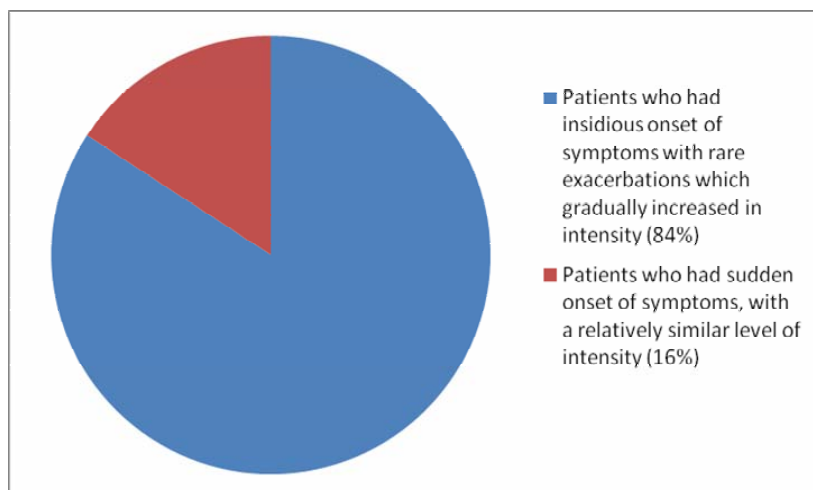


Figure 2. Symptoms onset (Most of the patients had an insidious onset of symptoms).

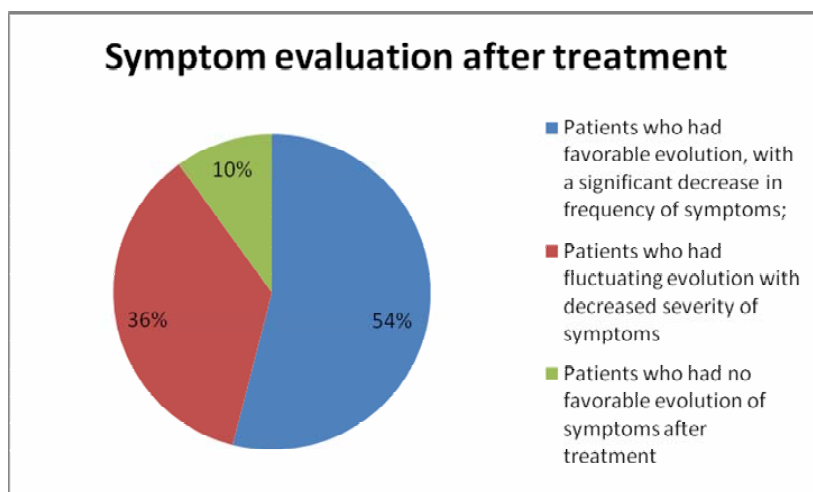


Figure 3. Symptoms evolution with medical treatment
(Most of the patients had a favorable evolution of symptoms with medical treatment).

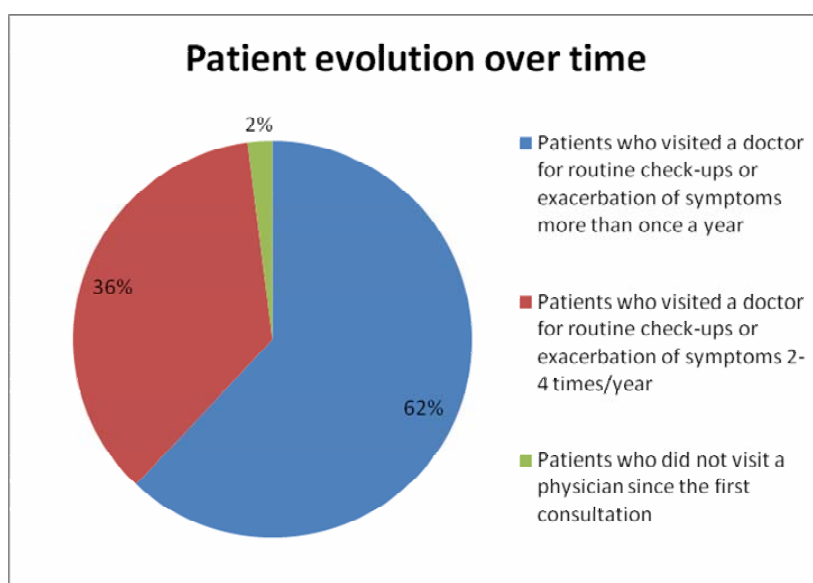


Figure 4. Patients evolution over time
(Most of the patients were presented to the doctor for control at least once a year).

Table III

Average severity of symptoms before and after treatment by IBS subtype

	IBS subtype		
	IBS-C	IBS C+D	IBS-D
Before treatment	8	8	9
After treatment	4	5	6

Table IV

Symptom severity before and after trimebutine or mebeverine monotherapy

	IBS subtype		
	IBS-C	IBS C+D	IBS-D
Before treatment	8	8	9
After treatment	6	5	7

Table V

Symptom severity before and after treatment with trimebutine or mebeverine in association with other drugs

	IBS subtype		
	IBS-C	IBS C+D	IBS-D
Before treatment	8	8	9
After treatment	4	5	6

The favorable evolution of symptoms was associated with the use of probiotics in combination ($p < 0.001$), but not in monotherapy ($p < 0.001$).

Table VI

Symptom severity before and after probiotic treatment

	IBS subtype		
	IBS-C	IBS C+D	IBS-D
Before treatment	8	8	9
After treatment	7	7	8

Table VII

Symptom severity before and after probiotics in combination with other drugs

	IBS subtype		
	IBS-C	IBS C+D	IBS-D
Before treatment	8	8	9
After treatment	4	5	6

Table VIII

Symptom severity before and after anxiolytics in combination with other drugs

	IBS subtype		
	IBS-C	IBS C+D	IBS-D
Before treatment	8	8	9
After treatment	4	5	6

Table IX

The incidence of depression in patients with IBS

Depression	Patients with depression	Patients without depression
Nr.	31	83
%	27.19	72.81

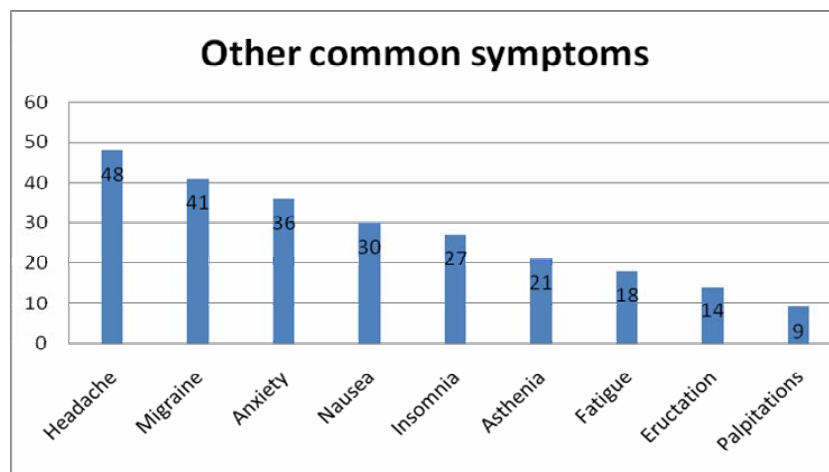


Figure 5. Common symptoms in IBS patients
(Headache is common among in IBS patients).

Table X
Diseases accompanying IBS

Accompanying diseases	Depression	Dyslipidemia	Hemorrhoidal disease	Fibromyalgia
Nr.	31	29	26	24
%	27.19	25.43	22.80	21

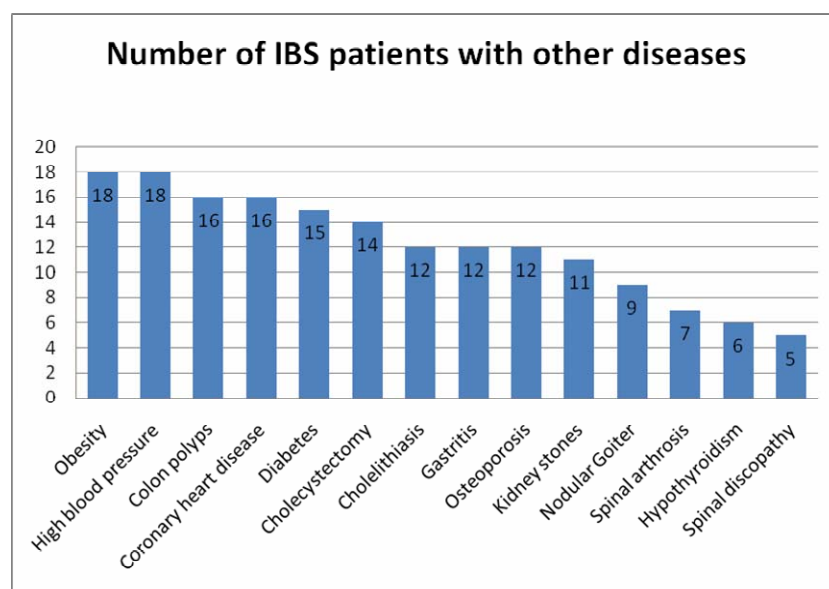


Figure 6. Other diseases on IBS patients
(Obesity, high blood pressure and colon polyps were relatively common in patients with IBS).

DISCUSSION

To our knowledge, this is the first study to report the results of a 4-year follow-up of a group of patients with IBS from Romania. It is known that we need a wide spectrum of diagnostic procedures to exclude other diseases, when suspecting IBS along with other gastrointestinal diseases. Previous studies have reported GI disorders and

other co-morbidities among patients with IBS, but many of these studies were conducted among ambulatory IBS patients [21, 22] and only a few studies were based on a group of hospitalized patients [23].

Patients diagnosed with IBS are predominant in urban areas.

The three main symptoms observed were: abdominal pain, bloating and bowel disorders.

20.17% of the followed patients had painful episodes daily, 91.2% of patients presented bowel disorders, most with predominant constipation and 18.4% of patients reported daily bloating, a significant number of them exhibited very troublesome manifestations of the disease, leading to reduced quality of life and impaired daily activities.

According to our results, the most common associated diseases were: depression (the most frequent disease associated with IBS), dyslipidemia, hemorrhoidal disease and fibromyalgia.

Depression has been described in numerous other studies that have focused on IBS as a common disease in these patients. Higher rates of anxiety and depression, and sleep problems have previously been recognized as factors associated with the diagnosis of IBS [24, 25]. Hemorrhoidal disease and dyslipidemia have not been described in literature as commonly found in patients with IBS, their increased incidence in our group of patients represents new information regarding the possible association with IBS. Fibromyalgia is a common investigated co-morbidity in patients with IBS [26, 27]. In this study, fibromyalgia has been recognized as co-morbidity in women only.

Patients with IBS often have headaches and migraines according to many studies [28-30]. Non-gastrointestinal symptoms are an important part of overall complaints of patients with IBS, fact which affects the diagnosis and treatment setting algorithm [31].

Diagnoses of thyroid disease and other digestive diseases, diabetes, dyslipidemia, kidney

stones, rheumatologic and cardiovascular diseases, were less commonly found in patients with IBS. Diagnosis of the associated diseases was established before or after the initial diagnosis of IBS. It would be interesting to analyze in future studies if patients being diagnosed with various other conditions prior to a diagnosis of IBS represented a risk factor for the occurrence of IBS.

Regarding the administered treatment, patients with predominance of constipation had a better response rate to drug therapy than those with predominance of diarrhea. The trimebutine or mebeverine in combination with anxiolytics and probiotics (trimebutine 300 mg/day + alprazolam 0.25 mg, 1/2-1/2-1 tb/day + Eubiotic 1-0-1 tb/day) treatment was correlated with the best long-term improvement of symptoms, monotherapy being associated with fluctuating symptoms. Patients diagnosed with depression and anxiety had a lower response rate to treatment.

From the perspective of literature, new aspects are represented by the common association in our group of IBS patients with hemorrhoidal disease and dyslipidemia, predominance of IBS-C and the treatment given to the patients. Predominantly urban areas, the 3 major symptoms described above, the association with depression and fibromyalgia are issues frequently described in the literature. The main limit of this study was the fact that it was conducted in a single tertiary center.

Regarding on what may also be investigated, we consider useful to analyze a bigger lot of IBS patients, from several centers, over a larger follow-up and comparing data with our results.

Scopul studiului. Există puține date în literatură privind evoluția pacienților cu Sindrom de intestin iritabil (SII) și alte boli asociate. Prin urmare, noi am studiat evoluția pacienților cu SII într-un singur centru terțiar, într-un interval mai mare de timp.

Metode. A fost realizat un studiu retrospectiv bazat pe studierea arhivei pacienților cu SII din clinica noastră. Am analizat datele privind simptomele, terapia administrată pacienților și bolile asociate, toate acestea fiind consemnate la vizitele de urmărire pe o perioadă de patru ani (2008-2011).

Rezultate. Au fost incluși în studiu 114 pacienți cu SII diagnosticați pe baza criteriilor Roma III (29 de bărbați și 85 de femei), cu vârste între 19-85 ani (vârsta medie: 43,45 ani). Au predominat pacienții din mediul urban. Principalele trei simptome înregistrate au fost: durerea abdominală, tulburările tranzitului intestinal (constipație, diaree) și balonarea. SII cu predominanța constipației (SII - C) este asociat cu o evoluție favorabilă a simptomelor după tratament (creșterea numărului de scaune, scăderea intensității durerii abdominale și a balonării) iar SII - cu predominanța diareei (SII - D) este asociat cu simptome de intensitate variabilă după tratament ($p = 0,031$). Utilizarea trimebutinei sau mebeverinei în asociere cu alte medicamente timp de o lună se corelează cu o evoluție favorabilă

a simptomelor după tratament, iar monoterapia este asociată cu fluctuanța simptomelor ($p < 0,001$). Evoluția favorabilă a simptomelor este asociată cu utilizarea de probiotice în combinație, dar nu și în monoterapie ($p < 0,001$). Evoluția favorabilă a simptomelor este de asemenea asociată cu utilizarea anxiolitice în combinație cu alte medicamente. Persistența simptomelor după tratament a fost corelată cu prezența sau absența depresiei. Absența depresiei a fost corelată cu o evoluție favorabilă a simptomelor ($p = 0,005$). SII-C este asociat la limită (semnificație marginală), cu boala hemoroidală ($p = 0,56$). 33 de pacienți (29%) – au primit monoterapie (trimebutină sau mebeverină sau probiotice; 81 de pacienți (71%) – au primit terapie combinată: (trimebutină sau mebeverină sau probiotice + anxiolitice sau inhibitori ai pompei de protoni (IPP), antiinflamatoare nesteroidiene (AINS) sau spasmolitice. Cele mai frecvente boli asociate observate la pacienții cu SII au fost: depresia (27,19%), dislipidemia (25,43%), boala hemoroidală (22,80%) și fibromialgia (21%).

Concluzii. Cea mai mare rată de răspuns a fost obținută după administrarea tratamentului cu trimebutină sau mebeverină + anxiolitice + probiotice. Cea mai frecventă boală asociată cu SII a fost depresia. Alte boli cu o incidență ridicată: dislipidemia, boala hemoroidală și fibromialgia. Sunt necesare studii suplimentare pentru a analiza legătura dintre SII și unele boli asociate.

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