A Physiologic Events' Cascade, Irritable Bowel Syndrome, is Significantly Associated with Chronic Gastritis, Hemorrhoid, Urolithiasis, and Depression

Bir fizyolojik kaskat olan iritabl bağırsak sendromu; kronik gastrit, hemoroid, ürolithiyazis ve depresyon ile ilişkilidir

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SUMMARY

Objectives: About one third of people report recurrent upper abdominal discomfort, and irritable bowel syndrome (IBS) is probably associated with most of the underlying pathologies.

Materials and Methods: We took consecutive patients admitted to the Emergency Department because of upper abdominal discomfort. IBS is diagnosed according to Rome II criteria in the absence of red flag symptoms, which are not typical for IBS. Other underlying causes of upper abdominal discomfort were detected and results were compaired between the cases with and without IBS.

Results: One hundred and twenty patients with IBS and 138 patients without were studied. Although 61.6% (n=74) of the IBS cases were female, this ratio was 42.0% (n=58) in patients without IBS (p<0.001). On the other hand, chronic gastritis (CG) was detected in 72.5% (87) of cases with IBS, whereas this ratio was 36.2% (50) in patients without (p<0.001). Similarly, although the prevalence of hemorrhoid was 33.3% (40) in the IBS cases, it was 15.2% (21) in the other group (p<0.001). Beside that, urolithiasis was detected in 17.5% (21) of the cases with IBS and in 11.5% (16) of the cases without (p<0.05). Additionally, the prevalence of depression was higher in the IBS group (p<0.001).

Conclusion: Relationships between IBS and CG, hemorrhoid, urolithiasis, and depression are significant, and IBS is a cascade of many physiologic events, being initiated with psychological disturbances-like many stresses and eventually terminating with gut dysfunction. Keeping in mind these associations will be helpful for physicians during prevention, treatment, and follow up of these patients.

Key words: Chronic gastritis; depression; hemorrhoid; irritable bowel syndrome; urolithiasis.

ÖZET

Giriş: *İnsanların üçte biri karnın üst bölgesinde tekrarlayan ağrılardan yakınırlar ve bu hastaların çoğunda altta yatan olası patoloji iritabl bağırsak sendromu'dur (İBS).*

Gereç ve Yöntem: *Acil servise üst abdomen ağrısı nedeniyle başvuran tüm hastalar ardışık olarak çalışmaya alındı. İBS, olası hayatı tehdit edebilecek karın ağrısı nedeni ile başvuran hastalar hariç Rome II kriterlerine göre koyuldu. Üst abdomen ağrısı diğer nedenleride saptandıktan sonra, sonuçlar İBS olan ve olmayan hastalar arasında karşılaştırıldı.*

Bulgular: *Çalışmaya İBS tanısı koyulan 120 hasta ile konulmayan 138 hasta alındı. İBS tanısı konulan hastaların %61.6'sı (n=74), İBS tanısı koyulmayan hastaların ise %42'si (n=58) kadındı (p<0.001). Kronik gastrit İBS grubunun %72.5'inde (n=87), saptanmayan hastalarınsa %36.2'sinde (n=50) mevcuttu (p<0.001). Benzer olarak hem hemoroid prevalansı (%33.3, n=40 vs %15.2, n=21; p<0.001) hem de ürolithiyazis prevalansı (%17.5, n=21 vs %11.5, n=16; p<0.005) İBS saptanan hastalarda anlamlı olarak daha yüksekti. Ayrıca depresyon prevalansı da İBS grubunda anlamlı olarak daha yüksekti (p<0.001).*

Sonuç: *İritabl bağırsak sendromu birçok fizyolojik olayın rol oynadığı fizyolojik bir kaskattır; stress gibi psikolojik sorunlarla başlar ve bağırsak disfonksiyonu ile sonuçlanır. İBS kronik gastrit, hemoroid, ürolithiyazis ve depresyon ile ilişkilidir. Bu ilişkileri akılda tutmak İBS'nin hekimler tarafından tanınıp engellemesinde veya tedavi edilmesidinde faydalı olabilir.*

Anahtar sözcükler: *Depresyon; hemoroid; iritabl bağırsak sendromu; kronik gastrit; ürolithiazis.*

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Introduction

When asked specifically, about one third of people report recurrent upper abdominal discomfort and most of applications to primary health centers are due to this complaint.[1] Irritable bowel syndrome (IBS), chronic gastritis (CG), gastroesophageal reflux disease (GERD), esophagitis, duodenal and gastric ulcers, erosive gastritis and duodenitis, lactose intolerance, giardiasis, cholelithiasis, celiac disease, chronic pancreatitis, and malignancies are found among possible causes of this complaint, but probably IBS and CG are the most commonly diagnosed ones.

On the other hand, flatulence, periods of diarrhea and/or constipation, repeated toilet visits due to urgent evacuation or early filling sensation, excessive straining, feeling of incomplete evacuation, frequency, urgency, reduced feeling of well being, and disturbed social life due to the gastrointestinal and urinary tract symptoms are often reported by IBS patients. In addition to these complaints, it seems that IBS patients usually suffer from chonic gastritis, hemorrhoid, urolithiasis, and depression. We tried to understand whether or not there are significant relationships between IBS and the above disorders here.

Material and Methods

Patients admitted to the Emergency Department of the Mustafa Kemal University between January and October 2007 because of upper abdominal discomfort were consecutively enrolled to the study. A routine check up procedure including serum levels of IgA, urinalysis, fresh fecal sample examination, abdominal X-ray graphy in supine position, and abdominal ultrasonography was performed, and past medical history including alcohol consumption, hyperuricemia, urolithiasis, and requirement to use a antidepressive drug at least for a period of six-month were established. Body mass index (BMI) of each case was calculated. Weight in kilograms is divided by height in meters squared, and obesity is defined as a BMI of 30 kg/m^2 or greater.[2] A questionnaire for IBS was performed, and IBS is diagnosed according to Rome II criteria (Table 1) in the absence of red flag symptoms, which are not typical for IBS, such as pain or diarrhea that often awak-

Table 1. *Rome II criteria.*[25]

IBS can be diagnosed based on at least 12 weeks, which need not be consecutive, of the preceding 12 months there was abdominal discomfort or pain that had two out of three of these features.
- Relieved with defecation; and/or
- Onset associated with a change in frequency of stool; and/or
- Onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of IBS:
- Abnormal stool frequency (for research purposes, "abnormal" may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week);
- Abnormal stool form (lumpy/hard or loose/watery stool);
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- Bloating or feeling of abdominal distention.

Supportive symptoms of IBS:
- A) Fewer than three bowel movements a week
- B) More than three bowel movements a day
- C) Hard or lumpy stools
- D) Loose (mushy) or watery stools
- E) Straining during a bowel movement
- F) Urgency (having to rush to have a bowel movement)
- G) Feeling of incomplete bowel movement
- H) Passing mucus (white material) during a bowel movement
- I) Abdominal fullness, bloating, or swelling

Diarrhea-predominant: At least 1 of B, D, F and none of A, C, E; or at least 2 of B, D, F and one of A or E.
Constipation-predominant: At least 1 of A, C, E and none of B, D, F; or at least 2 of A, C, E and one of B, D, F.
Red flag symptoms which are not typical of IBS:
- Pain that awakens/interferes with sleep
- Diarrhea that awakens/interferes with sleep
- Blood in the stool (visible or occult)
- Weight loss
- Fever
- Abnormal physical examination

Table 2. *Comparison of the cases with and without irritable bowel syndrome.*

Variable	Cases with IBS*	Cases without IBS	p
Number	120	138	
Mean age and range (year)	40.4±15.3 (15-86)	41.2±16.1 (15-80)	>0.05
Female ratio	61.6% (74)	42.0% (58)	<0.001
Chronic gastritis	72.5% (87)	36.2% (50)	<0.001
Hemorrhoid	33.3% (40)	15.2% (21)	<0.001
Urolithiasis	17.5% (21)	11.5% (16)	<0.05
Depression	43.3% (52)	25.3% (35)	<0.001
Obesity	45 (37.5%)	48 (34.7%)	>0.05
Hyperuricemia	9 (7.5%)	12 (8.6%)	>0.05

*Irritable bowel syndrome.

ens/interferes with sleep, weight loss, fever, or abnormal physical examination findings. An upper gastrointestinal endoscopy was performed, and sample biopsies from distal esophageal, gastric, and duodenal regions were taken according to macroscopic appearances. CG is diagnosed histologically. Infiltration of monocytes into gastric mucosa is hallmark of the CG.[3] Additionally, microscopic examination shows stereotypical changes in epithelium such as degeneration, focal intestinal metaplasia, dysplasia, and glandular atrophy.[3] Additionally, duodenal contents were aspirated to search trophozoites of *Giardia lamblia*. Rectosigmoidoscopy was performed just for cases ever being symptomatic for hemorrhoid. A urine culture was obtained in all cases with pyuria. Hyperuricemia is diagnosed via serum uric acid value (greater than 6.0 mg/dL for women and 7.0 mg/dL for men)[4] and/or usage of any drug for it. Intravenous pyelography was performed just for suspected cases from presenting urolithiasis as a result of the urinalysis and abdominal X-ray graphy. So urolithiasis was diagnosed either by medical history or as a result of the current laboratory findings. Additionally, a test for lactose intolerance was performed. Fifty-gram lactose, given orally, causes diarrhea with abdominal bloating and discomfort within 30-minute, and a rise in blood glucose of less than 20 mg/dL in cases with lactose intolerance. Because of highly variable clinical severity of celiac disease and high sensitivity and specificity of IgA antiendomysial antibodies,[5] they were used as a screening test for celiac disease and jejunal biopsy was planned just for the antibodies positive cases to see absence of villi and elongated crypts. The IgA antiendomysial antibodies were determined by the immunofluorescent method using a preparation of primate GIT smooth muscle from IMMCO (USA) (evaluation: positive/negative, sensitivity 97-100%, specificity 90-100%). A detailed history for GERD was taken, and thinning of squamous mucosal layer and basilar cell hyperplasia are accepted as esophagitis. Columnar mucosal changes are features of Barrett's metaplasia. All histologic samples were evaluated by the same pathologist. Results were compared between the IBS positive and negative groups. Comparison of proportions was used as the method of statistical analysis.

Results

One hundred and twenty patients with IBS and 138 patients without IBS were studied. Their mean ages were 40.4±15.3 and 41.2±16.1 years, respectively (p>0.05). Although 61.6% (n=74) of the IBS cases was female, this ratio was 42.0% (n=58) in the patients without IBS. So IBS was observed more frequently in females (p<0.001). On the other hand, CG was detected in 72.5% (n=87) of cases with IBS, whereas this ratio was 36.2% (n=50) in the patients without IBS (p<0.001). Similarly, although the prevalence of hemorrhoid was 33.3% (n=40) in IBS cases, it was 15.2% (n=21) in the other group (p<0.001). Beside that, urolithiasis was detected in 17.5% (n=21) of the cases with IBS and in 11.5% (n=16) of the cases without IBS (p<0.05). The difference between the two groups was significant according to depression, too and the prevalence of depression was also higher in the IBS group (43.3%, n=52 vs 25.3%, n=35 p<0.001). On the other hand, when we compared the groups according to obesity and hyperuricemia as risk factors for urolithiasis, there were insignificant differences between two groups (p>0.05 for both) (Table 2). Twenty-seven cases with gastric and/or duodenal ulcers were detected in both groups totally, but none of them was malignant histologically. Fourteen cases with giardiasis were diagnosed via fresh fecal samples and duodenal fluid examinations totally, and duodenal contents were diagnostic alone in three cases, and only cysts but not trophozoites could be detected in samples. On the other hand, we detected no case with either a diagnosis of IgA deficit or IgA antiendomysial

Table 3. *Comparison of the upper abdominal discomfort cases with and without irritable bowel syndrome according to other gastrointestinal pathologies.*

Variable	Cases with IBS*	Cases without IBS	p
GERD†	11 (9.1%)	8 (5.7%)	> 0.05
Esophagitis	3 (2.5%)	4 (2.8%)	> 0.05
Barrett's metaplasia	1 (0.8%)	1 (0.7%)	> 0.05
Erosive gastritis and/or duodenitis	2 (1.6%)	1 (0.7%)	> 0.05
Gastric ulcer	5 (4.1%)	8 (5.7%)	> 0.05
Duodenal ulcer	6 (5.0%)	8 (5.7%)	> 0.05
Lactose intolerance	96 (80.0%)	102 (73.9%)	> 0.05
Giardiasis	6 (5.0%)	8 (5.7%)	> 0.05
Celiac disease	0	0	–
Cholelithiasis	33 (27.5%)	40 (28.9%)	> 0.05
Chronic pancreatitis	0	0	–
Malignancy	0	0	–

*Irritable bowel syndrome; †Gasroesophageal reflux disease.

antibodies positivity. Beside that, we detected GERD, esophagitis, Barrett's metaplasia, erosive gastritis and/or duodenitis, gastric and/or duodenal ulcers, lactose intolerance, giardiasis, and cholelithiasis in both groups, but not chronic pancreatitis or malignancy, and the differences between the groups were insignificant according to the pathologies above (Table 3).

Discussion

Approximately 10-20% of general population have IBS,[6] and as also shown here, it is more common among females for unexplained reasons. Psychological factors seem to precede onset or exacerbation of gut symptoms, and many potentially psychiatric disorders such as anxiety, depression, and sleep disorders frequently coexist with IBS.[7] For example, thresholds for sensations of initial filling, evacuation, urgent evacuation, and utmost tolerance, recorded via a rectal balloon, significantly decreased by focusing the examiners' attention on gastrointestinal stimuli by reading pictures of malignant gastrointestinal disorders in IBS cases, however no remarkable change was observed in the other group.[8] So although IBS is described as a physical - not psychological - disorder according to Rome II guidelines, psychological factors may be crucial for triggering of the physical disorder, IBS.

Although underlying causes of pathophysiologic changes remain unclear, low-grade inflammation and abnormal intestinal motility are accepted mechanisms altering gut functions and generating symptoms.[9] According to the Rome II criteria, IBS is not a disease in stead a functional disorder, and it is actually defined as a brain-gut dysfunction, but just as a personal opinion, IBS is a more complex condition than this view. Parallel to the high prevalence of CG of our study, Chadwick and colleagues studied role of inflammation in 77 of cases with IBS and colonic biopsies were taken for conventional histology and immunohistology. Thirty-eight had normal histology, 31 demonstrated microscopic inflammation, and eight fulfilled criteria for lymphocytic colitis. However, in the group with "normal" histology, immunohistology revealed increased intraepithelial lymphocytes as well as increased CD3+ and CD25+ cells in *lamina propria mucosae*, as evidences of immune activation. These features were even more evident in the microscopic inflammation group, who additionally revealed increased neutrophil, mast cell, and natural killer cells. All of these immunopathological abnormalities were most evident in the lymphocytic colitis group, who also demonstrated HLA-DR staining in crypts and increased CD8+ cells in *lamina propria mucosae*.[10] A direct link between immune activation and symptoms was provided by work of Barbara and colleagues, who demonstrated not only an increased prevalence of mast cell degranulation in colon, but also a direct correlation between proximity of mast cells to neuronal elements and pain severity in IBS.[11] In addition to these findings, there are some evidences for extension of the inflammatory process beyond mucosa. Tornblom and colleagues addressed this issue in ten patients with severe IBS by examining full-thickness jejunal biopsies obtained via laparoscopy.[12] They detected a low-grade infiltration of lymphocytes in myenteric plexus in nine cases, four of whom had an associated increase in intraepithelial lymphocytes and six demonstrated evidence of neuronal degeneration. Nine patients had hypertrophy of longitudinal muscles and seven had abnormalities in number and size of interstitial cells of Cajal. The finding of intraepithelial lymphocytosis was con-

sistent with the reports of Chadwick and colleagues in colon and of Wahnschaffe and colleagues in duodenum.[13] So IBS is a cascade of many physiologic events, being initiated with psychological disturbances like stresses and terminating with gut dysfunction.

Gastric acid is probably not involved in etiology, but psychological factors seem to be crucial for CG, too. Our result, indicating the significant relationship between CG and IBS, and the already known importance of psychological factors for IBS also support this idea. Clearly, diet is implicated as regards predisposition to constipation, colorectal cancers, and diverticular disease, however, a meaningful dietary role in CG is doubtful. Some dietary habits may be the triggering factor for CG but this relationship does not always seen even in the same individuals. The most important etiologic association of CG is chronic infection by bacillus *Helicobacter pylori* (*H. pylori*). Although *H. pylori* is linked to CG, peptic ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue (MALT)- lymphoma[14] and it is recognised as a class I gastric carcinogen,[15] it infects over 50% of world population and only a small subset of infecteds experience *H. pylori*-associated disorders. Possible symbiotic relationships have been thought. The debate has been further intensified as some studies have opposed possibility that *H. pylori* infection may be beneficial for some humans. This hypothesis is based on the elevated incidence of GERD, Barrett's esophagus, and adenocarcinoma of esophagus, following *H. pylori* eradication in some countries. Recent studies have shown that *H. pylori* infection protects against GERD and esophageal carcinoma. A current hypothesis about this issue is the presence of a nearly symbiotic and balanced relationship between the bacterium and human body. The colonization may either be beneficial or of low biological cost to the host. So the role of *H. pylori* in CG is obvious but the answer of this question 'why every patient with CG does not need to apply to doctor?' is unknown. On the other hand, a meaningful dietary role in IBS is doubtful, too. Many patients relate onset of symptoms to intake of food and often incriminate specific food items. On the other hand, debate continues regarding potential overlap between IBS and celiac disease.[16] It is evident that majority of celiac cases present later in life, usually with vague and non-specific gastrointestinal symptoms. Thus, in a previous study authors concluded that celiac disease must be considered in all new IBS cases regardless of the nature of presenting symptoms, especially in areas with high prevalence of celiac disease.[17] Whereas we were not able to diagnose any case of celiac disease in the 258 study cases. Additionally, although we searched for lactose intolerance in all study cases, there was not a significant difference between the cases with and without IBS. So the exacerbation of IBS with specific food items may actually be a result of the significant association of the disease with CG, and we think CG is one of the terminating points of the physiologic events' cascade, IBS.

In addition to the bleeding, pain, soiling, and prolapse, many patients with grade 3-4 hemorrhoids have concomitant bowel symptoms, possibly associated with IBS.[18] Similarly, we detected a highly significant association between IBS and hemorrhoid here. Periods of constipation, repeated toilet visits, excessive straining, feeling of incomplete evacuation, and the possible low-grade inflammation are found among possible causes of hemorrhoid in IBS cases.

Urolithiasis is an extremely common pathology, too and lifetime risk of nephrolithiasis is 12-15% for a white man and 5-6% for a white woman with an up to 50% of lifetime recurrence ratio.[19] Although the urolithiasis may present in the absence of hematuri in a person, we detected the ratios of urolithiasis as 15.0% (19 cases) and 13.6% (18 cases) in men and women, respectively, in cases with hematuria. This point may be one of our limitation points in the study. Approximately 80% of the stones are composed of calcium oxalate (CaOx) and calcium phosphate (CaP), and CaOx is the main constituent of them. Beside that, 10% of struvite (magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease) and 9% of uric acid stones are seen. Majority of the CaOx stone formers suffer from no systemic disease,[20] and minority of the patients have primary hyperparathyroidism or some other disorders of calcium metabolism, hyperoxaluria secondary to bowel disease (enteric hyperoxaluria), or genetic disorders of oxalate metabolism (primary hyperoxaluria). Patients with chronic diarrheal illnesses such as ulcerative colitis and Crohn's disease can develop enteric hyperoxaluria, which results in an increased risk of renal stones.[21] It is often thought that oxalate is the primary problem in these patients, since excess oxalate is absorbed through the inflamed bowel wall. Similarly, low-grade inflammation induced increased absorption of oxalate may be the development mechanism of the urolithiasis in IBS. Although indirectly, increased oxalate absorption induced urolithiasis has also been shown previously.[22,23] So the giant gap about the underlying etiologies of CaOx stone formers may be explained by the high incidance of IBS in society. Here we additionally compared the IBS and urolithiasis groups according to hyperuricemia and obesity, but the differences were insignificant. As another hypothesis about the development mechanism of urolithiasis in IBS, diarrheal fluid

losses induced low urinary pH and citrate levels increase urinary CaOx and uric acid supersaturations, since citrate may inhibit calcium crystallization by binding to it. Uric acid stones are not easily seen on X-ray graphy whereas seen as filling defects on intravenous pyelography. Additionally, some types of bacteria can provoke urinary supersaturation and modify the environment, thus leading to formation of crystal deposits that may be a factor promoting urolithiasis. However, none of our cases with presenting urolithiasis gave a positive culture result. A further problem for IBS patients is urine supersaturation. Some of them restricts their fluid intake to control diarrhea and consequently has lower urinary volume. On the other hand, in another study relative risk of developing IBS was detected as 2.48 times higher in patients with urolithiasis than in those without, and authors concluded that urolithiasis should be considered as an etiological factor during management of IBS.[24] But actually we think that urolithiasis is one of the terminating points of IBS, as a cascade of many physiological events, because of its prolonged nature, urinary tract involvement, and frequently observed urinary symptoms even in the absence of any presenting urolithiasis, but basis for these associations is unclear yet.

As a conclusion, the relationships between IBS and CG, hemorrhoid, urolithiasis, and depression are significant, and IBS is a cascade of many physiologic events, being initiated with psychological disturbances-like many stresses and eventually terminating with gut dysfunction. The giant gap for the etiology of most of urolithiasis cases may be explained by the high incidance of IBS in society. Keeping in mind these associations will be helpful for physicians during prevention, treatment, and follow up of these pathologies.

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