A Physiologic Events' Cascade, Irritable Bowel Syndrome, may Even Terminate with Urolithiasis

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(Received April 13, 2006; Accepted May 8, 2006)

Aim: Approximately 10–20% of general population has irritable bowel syndrome (IBS) and/or urolithiasis (U) and it seems that there is a significant association between them. Methods: We randomly took consecutive patients with and without IBS, among the cases applying to internal medicine polyclinic. U was diagnosed either by medical history or current findings. Results: Female/male ratio of IBS cases was 1.62. On the other hand, U was detected in 111 cases, totally, and female/male ratio was 0.94. So the rates of U were 13.7 and 15.2% in female and males, respectively. As a significant finding, U was detected in 61 (17.9%) of cases with IBS, whereas this ratio was 11.6% (50 in number) among the cases without ($p < 0.01$). On the other hand, there was no significant difference between groups of IBS and U according to obesity and hyperuricemia ($p > 0.05$ for both). Conclusions: Although IBS predominantly keeps females, relationship between IBS and U is still significant. IBS is probably a cascade of many physiological events, being initiated with infection, inflammation, psychological disturbances like many stresses and eventually terminating with gut dysfunction. So U may be one of the terminating points of the physiological events' cascade, IBS. By this way, the giant gap about the underlying etiologies of most of U cases may be explained by the high incidance of IBS in society. Keeping in mind this association will be helpful during prevention, treatment, and follow up of these pathologies.

Key words —— irritable bowel syndrome, urolithiasis, lactose intolerance, celiac disease

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INTRODUCTION

When specifically asked, about every third of people report upper abdominal discomfort and most of applications to primary health center and internal medicine polyclinics are due to this complaint.[1)] Irritable bowel syndrome (IBS), chronic gastritis (CG), gastroesophageal reflux disease (GERD) without esophagitis, esophagitis, duodenal and gastric ulcers, erosive gastritis and duodenitis, lactose intolerance, cholelithiasis, malignancy, giardiasis, celiac disease, and chronic pancreatitis are found among possible causes of this complaint, but probably IBS is the most commonly diagnosed one among all.

Excessive straining, feeling of incomplete evacuation, repeated toilet visits due to urgent evacuation or early filling sensation, flatulence, periods of diarrhea and/or constipation, frequency, urgency, reduced feeling of well being, and disturbed social life caused by both gastrointestinal and urinary tract symptoms are often reported by IBS patients. In addition to these complaints, it seems that IBS patients usually suffer from urolithiasis (U). We tried to understand whether there is a significant relationship between them, here.

MATERIALS AND METHODS

We randomly took consecutive patients with and without IBS, among the cases applying to internal medicine polyclinic of the Dumlupinar University, between August and December 2005. Medical pasts including hyperuricemia and/or drug usage for it and U were learnt, and body mass indexes (BMI) were calculated to detect obese ones. Weight (in kilograms) is divided by square of height (in meters) to calculate BMI and obesity is defined as a BMI > 30. A questionnaire for IBS was performed and it was diagnosed according to Rome II criteria in the absence of red flag symptoms, which are not typical for IBS, such as pain or diarrhea that often awakens/interferes with sleep, weight loss, fever, or an abnormal physical examination. Routine hematologic and biochemical tests, urinalysis, and an abdominal X-ray graphy in supine position were performed. Additional intravenous pyelography (IVP) was performed just in suspected cases from presenting U as a result of the urinalysis and abdominal X-ray graphy. So U was diagnosed either by medical history or as a result of current laboratory findings. A urine culture was obtained in all cases with pyuria.

Table 1. Comparison of Cases with and without Irritable Bowel Syndrome

	Number and sexual distribution	Mean age, standard deviation, and range (year)	Number and percentage of cases with lactose intolerance	Number and percentage of cases with celiac disease	Number and percentage of cases with U[b]
Cases with IBS[a]	339 (210 female)	40.43 ± 15.03 (15–86)	275 (81.12%)	1 (0.29%)	61 (17.99%)
Cases without IBS	429 (183 female)	41.21 ± 16.06 (15–80)	335 (78.08%)	1 (0.23%)	50 (11.65%)
p-value			> 0.05	> 0.05	< 0.01

a) Irritable bowel syndrome. *b*) Urolithiasis.

Table 2. Comparison of Cases with Irritable Bowel Syndrome and Urolithiasis

	Number and sexual distribution	Mean age, standard deviation, and range (year)	Female/male ratio	Number and percentage (%) of cases with obesity	Number and percentage (%) of cases with hyperuricemia
IBS[a]	339 (210 female)	40.43 ± 15.03 (15–86)	1.62	32 (9.43%)	3 (0.88%)
U[b]	111 (54 female)	46.53 ± 13.97 (18–75)	0.94	13 (11.71%)	2 (1.80%)
p-value				> 0.05	> 0.05

a) Irritable bowel syndrome. *b*) Urolithiasis.

Hyperuricemia was diagnosed *via* serum uric acid value (> 7.0 mg/dl) and/or usage of any drug for it. A test for lactose intolerance was performed. Fifty gram lactose, given orally, causes diarrhea with abdominal bloating and discomfort within 30 min and a rise in blood glucose of < 20 mg/dl in cases with lactose intolerance. Because of highly variable clinical severity of celiac disease and high sensitivity and specificity of endomysial antibody (EMA), EMA was used as a screening test for celiac disease and jejunal biopsy was performed just in EMA positive cases to see absence of villi and elongated crypts. Comparison of proportions was used as method of statistical analysis.

RESULTS

Totally 768 patients, 339 with IBS and 429 without IBS, were studied. Threehundred and ninetythree of them were female and 375 were male. General properties of the cases with and without IBS were shown in Table 1. Mean age of IBS cases was 40 years and female/male ratio of them was 1.62. So IBS was observed as a more common disorder among females. On the other hand, U was detected in 111 cases, totally, and female/male ratio was 0.94 (Table 2). So the rates of U were 13.74 and 15.20% in female and males, respectively. Eight of 111 cases had U, now, but none of them gave a positive result of urine culture, and eleven of 111 cases had been operated before. Twentynine (26.12%) of U were bilateral, 38 (34.23%) were on the right, and 44 (39.63%) were on the left side. As a statistically significant finding, U was detected in 61 (17.99%) of cases with IBS, whereas this ratio was 11.65% (50 in number) among the cases without IBS ($p < 0.01$). On the other hand, there was no significant difference between groups of IBS and U according to obesity and hyperuricemia ($p > 0.05$ for both). Beside that we detected lactose intolerance in 275 (81.12%) of cases with IBS and 335 (78.08%) of cases without IBS ($p > 0.05$). Celiac disease was diagnosed in two cases, one (0.29) in IBS cases and one (0.23) in cases without, *via* EMA positivity and jejunal biopsy ($p > 0.05$).

DISCUSSION

Approximately 10–20% of general population has IBS[2] and, as also shown here, it is more common in 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.[3] 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 about malignant gastrointestinal disorders in IBS cases, however, no remarkable change was observed in nonpatient group.[4] So although IBS is described as a physical — not psychological — disorder according to Rome II guidelines, psychological factors may be crucial for initiation of the physical disorder.

Although underlying causes of pathophysiologic changes remain unclear, low grade mucosal inflammation and abnormal intestinal motility are accepted mechanisms altering gut functions and generating symptoms in IBS.[5] According to the Rome II criteria, IBS is not a disease, in stead a functional disorder and it is actually characterized as a brain-gut dysfunction but as a personal opinion, we think IBS as a more complex condition than this view. For example, Chadwick and colleagues studied role of inflammation in 77 IBS cases. 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 of "normal" histology, immunohistology revealed increased intraepithelial lymphocytes as well as increased CD3+ and CD25+ cells in lamina propria, 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 human leukocyte antigen (HLA)-DR staining in crypts and increased CD8+ cells in lamina propria.[6] 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.[7] 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 by means of laparoscopy.[8] 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 consistent with the reports of Chadwick and colleagues in colon and of Wahnschaffe and colleagues in duodenum.[9] So IBS may actually be a cascade of physiologic events, being initiated with infection, inflammation, psychological disturbances like many stresses and terminating with gut dysfunction.

On the other hand, U is an extremely common pathology, too and for example, lifetime risk of nephrolithiasis is 12–15% for a white man and 5–6% for a white woman with a lifetime recurrence rate of up to 50%.[10] We detected ratios of U as 15 and 13% in men and women, respectively. Approximately 80% of stones are composed of calcium oxalate (CaOx) and calcium phosphate (CaP) and CaOx is the main constituent of them, 10% of struvite (magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme urease), and 9% of uric acid (UA) stones. Majority of CaOx stone formers (SF) suffer from no systemic disease.[11] Some has primary hyperparathyroidism or other disorders of calcium metabolism, and others present with hyperoxaluria because of bowel disease (enteric hyperoxaluria) and 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 developing renal stones.[12] 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 mucosal inflammation induced increased absorption of oxalate may be the development mechanism of U in IBS. Although indirectly, increased oxalate absorption induced U had also been shown previously.[13,14] So the giant gap about the underlying etiologies of CaOx SF may be explained by the high incidance of IBS in society. Here we additionally compared the IBS and U groups according to hyperuricemia and obesity but the differences were insignificant. As another hypothesis about the development of U in IBS, diarrheal fluid losses induced low urinary pH and citrate levels increase urine CaOx and UA supersaturations, since citrate may inhibit calcium crystallization by binding to it. UA stones are not easily seen on x-ray graphy whereas seen as filling defects on IVP. 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 U. However, none

of our cases with presenting U gave a positive result of urine culture. A further problem for IBS patients is urine supersaturation. Some of them restricts their fluid intake to control diarrhea and consequently has lower urine volumes. On the other hand, in another study relative risk of developing IBS was detected as 2.48 times higher in patients with U than in those without, and U should be considered as an etiological factor during management of IBS.[15] But actually we think U as one of 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 current U, but basis for these associations is still unclear.

As a conclusion, although IBS predominantly keeps females as a difference from U, the relationship between them is still significant. IBS is probably a cascade of many physiological events, being initiated with infection, inflammation, psychological disturbances like many stresses and eventually terminating with gut dysfunction. So U may be one of the terminating points of the physiological events' cascade, IBS. By this way, the giant gap about the underlying etiologies of most of U cases may be explained by the high incidance of IBS in society. Keeping in mind this association will be helpful during prevention, treatment, and follow up of these pathologies in internal medicine and urology polyclinics.

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