Prevalence of irritable bowel syndrome-like symptoms in ulcerative colitis patients with clinical and endoscopic evidence of remission: prospective multicenter study

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Short title: Prevalence of IBS-like symptoms in UC patients

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Abstract

Objective

Irritable bowel syndrome (IBS)-like symptoms are often found in ulcerative colitis (UC) patients in remission. However, the prevalence of those symptoms in UC patients with endoscopic evidence of remission shown by mucosal healing remains unknown.

Material and methods

IBS diagnosis was evaluated by questionnaire results according to the Rome III criteria. Clinical remission was assessed by clinical activity index (CAI) , while endoscopic remission was evaluated by endoscopic index (Matts grade).

Results

We enrolled 172 patients in clinical remission (CAI≤4) , after excluding 36 for incomplete questionnaire results or non-remission findings, as well as 330 control subjects. Of the 172 UC patients, 46 (26.7%) met the Rome III criteria, which was a significantly higher rate than the controls (4.8%). The prevalence rate of IBS-like symptoms in UC patients with endoscopic remission findings (Matts grade ≤2) was 25.6%, which was similar to that of those with clinical remission. When endoscopic remission was defined as Matts grade 1, the prevalence rate of IBS-like symptoms was decreased to 15.4%, though that rate remained significantly higher than that of the control subjects.

Conclusions

The prevalence of IBS-like symptoms in UC patients with clinical and endoscopic remission findings was significantly higher than that of control subjects. Furthermore, that prevalence rate in patients with complete endoscopic remission was decreased. These findings suggest that residual low grade inflammation may influence the presence of IBS-like symptoms in UC patients in remission.

Key words

clinical remission; endoscopic remission; IBS-like symptoms; ulcerative colitis

Introduction

Irritable bowel syndrome (IBS) is a chronic functional disorder of the intestinal tract in the absence of organic abnormalities and characterized by clinical symptoms such as abdominal pain and discomfort, along with alterations in bowel habits (1-5). IBS represents a highly prevalent intestinal disease that affects around 10-15% of adults in most countries and a number of studies have demonstrated that psychological distress, disturbances of intestinal motility, and visceral hypersensitivity are closely associated with its pathogenesis(6-8). In recent years, the role of gastrointestinal infection has been investigated as a new aspect in the etiology of IBS, with low-grade gut mucosal inflammation and immune activation following an episode of acute gastroenteritis currently recognized as important factors underlying the pathogenesis of the disorder (6, 9-14).

Ulcerative colitis (UC) and Crohn's disease (CD) are two major forms of inflammatory bowel disease (IBD), and characterized by chronic immune-mediated intestinal disorders of unknown etiology. Although the disease entity IBD is essentially distinguished from IBS based on the presence or absence of intestinal organic lesions, IBS-like symptoms are often reported by IBD patients (15). Recent epidemiological studies have revealed that an episode of gastroenteritis and the presence of IBS are risk

factors for development of IBD (16, 17). In addition, etiological factors regarding immune regulation, genetic polymorphisms, and responses to luminal microbial pathogens partially overlap between IBS and IBD (18). Those findings suggest that overlapping etiological factors may influence the presence of IBS-like symptoms in IBD patients.

Numerous studies have investigated the presence of IBS-like symptoms in UC patients without evidence of ongoing disease activity (19-23). A recent meta-analysis indicated that IBS-like symptoms occurred in approximately 30% of UC patients in remission (15). In their studies analyzed, remission was mainly defined by evaluating clinical symptoms. However, the prevalence of IBS-like symptoms in UC patients with endoscopic evidence of remission shown by mucosal healing remains unknown. In the present study, we investigated UC patients with clinical as well as endoscopic remission evidence, and evaluated the presence of IBS-like symptoms.

Materials and Methods

Patients and control subjects

This study was prospectively conducted from May 2011 to February 2012 at 1 university hospital and 3 general hospitals in Japan. Diagnoses of UC were based on standard clinical, endoscopic, and histological criteria. At each hospital, all UC patients (≥18 years old) with a clinically good appearance as defined by their attending physician were assessed in this study, while patients with hematochezia, a history of colectomy or C-reactive protein > 0.5mg/dl were excluded. Thus 172 were enrolled in this study. In addition, consecutive individuals who underwent a general medical check-up at Matsue Seikyo Hospital were enrolled as healthy control subjects. The study protocol was approved by the institutional ethics committee of each hospital.

Evaluation of IBS- and FD-like symptoms

After obtaining written consent from each patient and control subject, the presence of IBS-like symptoms was evaluated by questionnaire results according to the Rome III criteria. The Japanese version of the questionnaire used in this study was validated in our previous study (2).

Definition of clinical and endoscopic remission

Disease activity was assessed using clinical activity index (CAI) (Rachmilewitz index; 24) and Matts grading (25). The Matts grading system is as follows: 1. normal; 2. mild granularity of the mucosa with mild contact bleeding; 3. marked granularity and oedema of the mucosa, contact bleeding, and spontaneous bleeding; and 4. severe ulceration of mucosa with hemorrhage. Clinical remission was defined as a CAI score of ≤4 for at least 6 months, while endoscopic remission was defined as Matts grade ≤2 for at least 3 months. Questionnaire results and endoscopic findings for the patients were carefully evaluated by 2 IBD experts (S.I. and Y.K.).

Statistical analysis

Differences for prevalence of IBS-like symptoms between the UC and control groups were evaluated using a chi-squared test. A *P* value of <0.05 was considered to be significant. All calculations were performed with SPSS version 19.0 for Windows.

Results

Study subjects

A total of 172 UC patients with clinical evidence of remission were enrolled in the present study by their physicians, then carefully screened by 2 IBD experts prior to the present analysis. Of them, 43 agreed to undergo a colonoscopy examination, with those results showing that 39 had endoscopic evidence of remission (Matts grade ≤2). In addition, 330 healthy subjects were enrolled during the study period as a control group. A flow chart of the present study patients is presented in Figure 1, while the baseline characteristics of the patients and controls are shown in Table 1. Eight patients who underwent tapering of steroid administration after achieving clinical remission were also enrolled. There were no differences in regard to gender and average age between the groups.

Prevalence of IBS-like symptoms in UC patients with clinical evidence of remission

The prevalence rate of IBS-like symptoms in the UC patients with clinical evidence of remission (CAI ≤4) was 26.7% (46/172, 95% confident interval (CI) :21.0-33.8%), and that in control subjects was 4.8% (95% CI: 3.0-7.7%) (26.7% vs 4.8%, OR: 7.17, 95% CI: 3.94-13.0, p <0.01) (Figure 2A). IBS can be sub-classified into several categories using the Rome III criteria based on the predominant bowel symptom of the patient (1).

The prevalence rate of each IBS type (IBS-D, diarrhea predominant; IBS-C, constipation predominant; IBS-M, mixed, IBS-U, unspecified) in the patients and controls are shown in Figure 2B. A high rate of prevalence of IBS-U (41.3%) was found in the UC patients with IBS-like symptoms as compared to the control group.

Prevalence of IBS-like symptoms in UC patients with endoscopic evidence of remission

Of the 39 UC patients with endoscopic evidence of remission (Matts grade ≤2), 10 met the Rome III criteria (25.6%, 95%CI: 14.6-41.1%), which was similar to that found in UC patients with clinical evidence of remission (26.7%). The prevalence rate of IBS-like symptoms was significantly higher than that in the control subjects (25.6% vs. 4.8%, OR6.77, 95%CI: 2.87-16.0, p <0.01, Figure 3). When endoscopic remission was strictly defined as Matts grade 1, the prevalence rate decreased to 15.4% (95%CI: 4.3-42.2%) and there was no statistical difference as compared to the control group (15.4% vs. 4.8%, OR 3.57, 95%CI 0.83-15.8, p =0. 14, Figure 3). In addition, we did not find a statistical difference between Matts grade ≤2 and 1 patients in regard to the prevalence rate of IBS-like symptoms(25.6% vs 15.4%, OR 1.9, 95%CI: 0.39-8.80) .

Discussion

The present results indicate that the prevalence of IBS-like symptoms in UC patients with clinical and endoscopic evidence of remission is significantly higher than that in healthy individuals. In addition, we precisely analyzed endoscopic findings in UC patients and found that the prevalence rate in those with complete endoscopic remission (Matts grade 1) was lower than that in patients with clinical findings of remission. These results suggest that the presence of IBS symptoms may be associated, at least in part, with residual low grade inflammation.

Previous studies have indicated that IBS symptoms often occur in UC patients in apparent remission (19-23). Although various criteria were used to define UC remission, a range of 9.1-46% of those patients in remission met the Manning or Rome II criteria for IBS (19-23). Halpin *et al*. recently performed a systematic review and meta-analysis of cross-sectional and case-control investigations, and finally analyzed 13 studies (1703 cases) to evaluate the prevalence of IBS-like symptoms in IBD patients (15). Their findings showed that the prevalence of IBS-like symptoms was significantly higher in IBD patients in remission (UC, 31%; CD, 41%) as compared to control cases. In the present case-control study, 172 UC patients and 330 control subjects were analyzed, in which the prevalence rate of IBS-like symptoms in UC patients (n=172)

with clinical remission findings was 26.7%, which was similar to the rate (31%) identified in the meta-analysis, as compared to 4.8% in the present control group (n=330). Thus, IBS-like symptoms commonly occur in UC patients in remission.

In previous studies, remission in UC patients was defined by various factors, including clinical activity, blood or fecal markers, and endoscopic or radiological findings. However, the prevalence of IBS-like symptoms in UC patients with endoscopic evidence of remission shown by mucosal healing has not been well reported (26). Although Isgar *et al*. and Simren *et al*. included endoscopic findings in remission criteria for UC, the definitions used in those studies were not sufficiently validated (19, 20). In the present study, Matts grade ≤2 was incorporated into the criteria for endoscopic remission, since that is widely used as a definition of mucosal healing in UC patients(27). Our analysis with this definition indicated that the prevalence rate of IBS-like symptoms in UC patients was 25.6%, which was similar to that when the definition of clinical remission was used (26.7%). In the present study, 4 of 43 patients with evidence of clinical remission were excluded from analysis due to the absence of mucosal healing (Matts 3), of whom all 4 had IBS-like symptoms. This finding suggests that approximately 10% of patients showing evidence of clinical remission do not have

colonic mucosal healing. In such cases, a colonoscopy examination or fecal calprotectin test may be useful for identifying these patients .

On the other hand, when endoscopic remission was strictly defined as Matts 1 (complete mucosal healing), the prevalence of IBS-like symptoms was decreased to 15.4%, though that rate remained higher than the rate seen in the control subjects. Since Matts grade 2 is defined as an endoscopic finding with residual mild mucosal damage, our findings suggest that low grade colonic inflammation may partially influence the presence of IBS-like symptoms in UC patients in remission. Similarly, Ansari *et al*. used the Mayo scoring system (0 or 1) for definition of endoscopic remission and found that the prevalence of IBS-like symptoms was 46% (21) , which was relatively higher than other previous reports. Since Mayo 1 includes endoscopic findings of mild mucosal damage similar to Matts 2, that prevalence rate might be affected by residual low grade mucosal inflammation in UC patients. Recently, Keohane *et al*. reported that an increased level of fecal calprotectin, a surrogate marker of subclinical inflammation, was associated with the frequency of IBS-like symptoms in IBD patients in remission (28). That finding also suggests that the presence of these symptoms is dependent on low grade mucosal inflammation. However, we did not find a statistical difference in regard to the prevalence rate of IBS-like symptoms between patients defined as Matts 1

and ≤2. To confirm this finding, a study with a larger number of subjects who underwent a colonoscopy examination is required. Furthermore, fecal calprotectin testing may also be useful for clarifying the influence of mucosal low grade inflammation on development of IBS-like symptoms in UC patients with remission evidence. In addition, establishment of consensus among pathologists is needed for classifying intestinal low grade inflammation to distinguish it from normal mucosa.

IBS is recognized to be a common functional disorder in the absence of organic abnormalities. However, recent studies have demonstrated that low grade inflammation shown by infiltration of various immune cells occurs in the colonic mucosa of some IBS patients (29, 30), even though their endoscopic findings are normal. In the present study, IBS-like symptoms were noted in 15.4% of UC patients without active endoscopic findings (Matts grade 1). In those cases with normal endoscopic findings, it is unclear whether the IBS symptoms are affected by residual occult inflammation or mainly due to other causes, including dysfunction of functional mechanisms and psychological factors. Further studies are necessary to confirm this point.

The main limitation of this study is that the number of patients who underwent a colonoscopy was small, as those examinations were only conducted after receiving consent. Since the patients in clinical remission were in relatively good health as

compared to those in an active stage, it is understandable that they might not agree to undergo a colonoscopic examination after achieving remission. However, the low number of patients analyzed in our study might have affected the results. To confirm the influence of endoscopic findings on the presence of IBS-like symptoms in UC patients, it is important to analyze a large number of subjects who underwent a colonoscopy. In addition, the prevalence rate of IBS found in the control group was relatively low (4.8%), which was similar to the result of our recent study regarding the prevalence of IBS in Japanese subjects (4.4%) (2). Epidemiological studies using a validated symptom-based definition, such as that by Manning, and Rome criteria have demonstrated various prevalence rates of IBS ranging from 2.5% to 25% in general populations (4) . Thus, prevalence rates might vary depending on the study population, and methodology (criteria) and sampling techniques utilized. Furthermore, we did not investigate the influence of psychological factors on the presence of IBS-like symptoms. Since those are etiologically important for understanding such symptoms, they should be included in a future analysis.

In summary, we performed a prospective multi-center study to evaluate the presence of IBS-like symptoms in UC patients with clinical and endoscopic remission findings. Although the prevalence of IBS-like symptoms was significantly higher in the

patient group as compared to the control group, that rate was decreased after excluding patients with endoscopic findings of Matts grade 2. Our findings suggest that residual low grade mucosal inflammation has an influence on the presence of IBS-like symptoms in UC patients in remission.

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Figure legends

Figure 1.

Flow chart of patients in the present study.

Figure 2.

Prevalence (A) and subtypes (B) of IBS-like symptoms in UC patients with clinical remission findings, and healthy control subjects. *p <0.01 vs. Control. IBS-D, ⊡; IBS-C, ▨; IBS-M, ▨; IBS-U, ■.

Figure 3.

Prevalence of IBS-like symptoms in UC patients with clinical and endoscopic evidence of remission, and healthy control subjects. *p <0.01 vs. control.