

患者はそれ以上の患者に比較してSRを認めにくかった(22 vs 53%, $p < 0.05$)。調査開始時の身体化スコア、抑うつスコアが高い患者ほど、SRを認めにくかった。

結論：SRは、IBS症状重症度の変化よりも調査開始時の症状重症度によって影響される。また、医師患者関係あるいは合併する心理的異常はIBS患者の治療満足度に影響を及ぼす。以上の結果から、アウトカム評価を考える上で、IBS患者の治療満足度は症状重症度だけでなく、心身医学的要因によっても左右されうることが考慮しなければならないことが示唆された。

A. 研究目的

過敏性腸症候群(irritable bowel syndrome: IBS)は、頻度の高い消化器疾患である。IBSは生物学的指標が乏しい機能的疾患であることから、臨床器質疾患が考えにくい慢性の消化器症状に対して、除外診断としてIBSと診断されることも少なくない。現在、IBSの診断基準(Rome III基準)は便秘異常と排便によって軽快する腹痛あるいは腹部不快感を特徴とする自覚症状に基づく。そのため、IBS治療に当たっては、主症状の改善度あるいは治療満足度を指標にする場合が多い。治療満足度(Satisfactory Relief: SR)は、IBSをはじめ多くの疾患に関する臨床治療研究のprimary outcome評価として広く用いられている。

IBSは生命自体を脅かす疾患ではないものの、慢性的でかつ多彩な身体症状や精神症状を伴いやすいので、癌をはじめとした重篤な疾患に罹っているのではないかと憂慮している患者は少なくない。一方、治療者にとっては、訴えが多いIBS患者の理解が困難となりやすい。そのため、しばしば良

好な医師患者関係を築き難くなる。

これまでどのような要因がIBS患者の治療アウトカムに影響されるかについては詳細に検討されていない。本研究の目的は、IBS患者のSRは治療前の主症状重症度だけでなく、精神症状あるいは医師患者関係によって影響されうるという仮説を検証することである。本研究によって、IBSにおける心理社会的因子の役割が治療効果にどのように影響を及ぼすかを調査した。

B. 方法

IBSあるいは機能的消化管障害と診断された仙台市内の医療機関受診患者60例(女性56%、平均年齢45才)を対象とした。調査開始時に、IBS Severity Index (IBSSI)によって腹痛、腹部膨満感、便秘異常、日常生活支障度によるIBS重症度を、Brief Symptom Index 18 (BSI-18)によって身体化、抑うつ、不安症状からなる精神症状重症度を評価し、さらに主治医から症状に対する保証度(0-100点)の患者評価を求めた。さらに、調査6ヵ月後にIBSSI、BSI-18、SR、全般

改善度を評価した。先行研究に基づき、初回の IBSSI スコア (500 点満点) から軽症 (<175)、中等症 (175-300)、重症 (300<) の 3 段階に分類した。6 ヶ月後調査において、最近 7 日間の腹部症状が「満足に改善した」かまたは「この 7 日間症状がなかった」例を SR ありの responder とした。7 段階の全般改善度を同時に測定し、「非常によくなった」かまたは「幾分かよくなった」と自己評価した例を全般改善ありの responder と判定した。また、6 ヶ月後と初回調査の IBSSI スコアの比が 0.5 未満の例を 50% 症状改善ありの responder とした。

本研究は東北大学医学部倫理委員会の承認を得ており、全ての被験者から文書で本研究参加の同意を得た。

C. 結果

6 ヶ月後に SR を認めた患者は、60 例中 25 例 (42%) であった。全般改善ありの患者は 27 例 (45%) であり、50% 症状改善ありの患者は 16 例 (27%) であった。SR を認めるも、全般改善なしの患者が 25 例中 9 例、50% 症状改善なしの患者が 13 例存在した。調査開始時に症状が重症であった患者は、最も重症度スコアの改善が大きかった (軽症 -31 ± 17 点, 中等症 71 ± 21 点, 重症 117 ± 24 点) にも関わらず、最も SR を認めにくかった (軽症 55%, 中等症 42%, 重症 25%, Fig. 1)。調査開始時の身体化スコア、抑うつスコアが高い患者ほど、SR を認めにくかった (それぞれ $p < 0.01$,

Kendall' s tau-b test)。保証度が 50 点未満の患者 (18 例) はそれ以上の患者 (36 例) に比較して SR を認めにくかった (22 vs. 53%, $p < 0.05$, χ^2 -test, Table 1)。

D. 考察

現在広く用いられている IBS 治療における Satisfactory Relief (SR) によるアウトカム評価において、全般改善度あるいは 50% 症状改善による評価とは必ずしも一致しない。SR はまた、IBS 症状重症度の変化よりも調査開始時の症状重症度によって影響されうる。医師患者関係あるいは合併する心理的異常は IBS 患者の治療満足度に影響を及ぼしうる。

先行研究で身体化の程度が重度ほど IBS 症状が重症であることが報告されている。今回の研究結果によって、アウトカム評価においても身体化が治療改善に対する満足度に影響しうるということが明らかになった。

良好な医療者患者関係を築くことによって IBS 患者の治療反応性が良くなることが報告されている。また、IBS 患者の受療行動は様々な要因によって左右されうるが、医療者患者関係が受療行動に大きく影響する。すなわち、患者の医療者への信頼度が高いほど、治療中断あるいは複数の医療機関受診 (いわゆるドクターショッピング) の割合が少なくなる。患者の医療者に対する信頼を得るためには、IBS あるいは機能性消化管障害として積極的に診断を行うことが重要である。

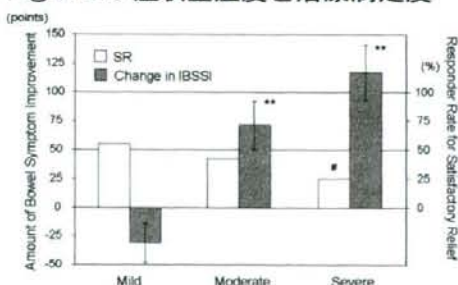
器質異常を鑑別するだけでなく、想定される病態仮説を患者に示して IBS の疾患概念を理解してもらうことが「保証」となる。本研究によってこの「保証」が患者の治療満足度を高めることに結びつく可能性が示された。

今後、さらなる研究によって患者特性、病態生理、治療内容、医師患者関係などが IBS に対する治療アウトカムにどのように寄与するかについて詳細な検討が望まれる。

E. 結論

以上の結果から、IBS 治療におけるアウトカム評価を考える上で、IBS 患者の治療満足度は症状重症度だけでなく、心理社会的要因によっても左右されうることを考慮しなければならないことが示唆された。

Fig.1. IBS 症状重症度と治療満足度



初回調査の重症患者群は、軽症患者群に比較して症状変化が有意に大きかった ($p < 0.01$) が、治療満足度は低い傾向を示した ($p = 0.07$)。

Table 1. 保証度と治療満足度の関係

	Reassurance		
	<50	50-100	Total
SR+	4 (22%)	19 (53%)	23
SR-	14	17	31
Total	18 (100%)	36 (100%)	54

($p < 0.05$, χ^2 -test)

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High Prevalence of Irritable Bowel Syndrome in Medical Outpatients in Japan

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Background and Goals: The prevalence of irritable bowel syndrome (IBS) among Japanese patients who visit hospitals departments of internal medicine is thought to be high. However, no clear statistical evidence has been provided to support such a claim. We tested the hypotheses that the prevalence of IBS in medical outpatients clinics in Japan is high, and that IBS patients feel more psychosocial stress than patients without IBS.

Study: The subjects in this study were 633 patients who visited participating physicians. Patients were asked to fill in the Japanese version of the Rome II Modular Questionnaire (RIIMQ) for IBS diagnosis, the Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ) for severity of the disease and the demographic questionnaire for perceived stress and life style.

Results: Rome II-defined IBS was diagnosed in 196 patients (31%). Analysis of variance revealed significant difference in the IBS scores of SIBSQ among IBS subjects (39.0 ± 11.1 , mean \pm SD), functional bowel disorder subjects (27.1 ± 10.2), and normal subjects (24.0 ± 10.0 , $P < 0.01$). The prevalence of IBS depending on age formed 2 peaks, one among adolescents and the other among the elderly. IBS patients had significantly more

perceived stress ($P < 0.0001$), irregular sleep habit ($P < 0.0001$), and irregular meal habit ($P < 0.0001$) than those without IBS.

Conclusions: The prevalence of IBS among medical outpatients in Japan is high (31%). IBS subjects among medically ill patients are thought to have more perceived stress and less regular life styles.

Key Words: irritable bowel syndrome (IBS), Rome II Modular Questionnaire, outpatient, stress

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Irritable bowel syndrome (IBS) is a very common and a chronic gastrointestinal (GI) disorder characterized by recurrent abdominal pain and altered bowel habits without major organic diseases by routine gastroenterologic examination.¹ IBS is a highly common disorder with a prevalence in Europe and North America of about 10% to 15% of the population.^{2,3} In GI practice, however, the prevalence of IBS accounts for 30% of patients in the United Kingdom.⁴ IBS has, therefore, become a serious issue for the medical economy in developed countries, including the United States and the United Kingdom,^{5,6} where a decline in the quality of life associated with disturbed activities at work,⁷ school, and daily life has been reported.^{8–10} In those countries, IBS is known to affect the negative impact on their quality of life.¹¹ In fact, psychosocial stress is repetitively reported as an aggravating factor of IBS.^{12,13}

For exact investigation of IBS, worldwide diagnostic criteria are indispensable.¹⁴ These criteria were proposed after the International Congress of Gastroenterology was held in Rome (Rome I).¹⁵ Rome II criteria^{16,17} were then established after a 7-year validation and evaluation period of Rome I. These criteria include the Rome II Modular Questionnaire (RIIMQ) developed by Rome Committee for clinical investigation and/or epidemiologic surveys.^{18,19}

Japan is a highly developed country with a culture, including diet and human relationships, different from

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those of western countries. Japan is also known as a country with increased level of psychosocial stress.²⁰ Despite predictions of high prevalence of IBS in Japan, an earlier preliminary study showed that the prevalence of Rome I-defined IBS in the consulters for healthcheck was only 3.6%, predominantly in males.²¹ However, this study was not based on a standardized method. In addition, in epidemiologic surveys in western countries, the prevalence of IBS was shown to be high among females.¹⁻⁵ As the establishment of a highly reliable and valid questionnaire for IBS in Japanese language was needed to compare data between western countries and Japan, we have recently established the Japanese version of RIIMQ. This Japanese version of RIIMQ has been shown to be reliable and valid.²² Although the prevalence of IBS among Japanese patients who visit hospitals departments of internal medicine is thought to be high, no clear statistical evidence, until now, has been provided to support such a claim.

The objectives of this study were (1) to confirm that the prevalence of IBS in Japanese outpatients who visit hospitals departments of internal medicine is high and (2) to verify the hypothesis that IBS subjects feel more psychologic stress than subjects without IBS.

SUBJECTS AND METHODS

Subjects

The subjects were patients who visited participating physicians in a Nation-wide Epidemiological Research Study conducted by the IBS Club in September 2002. Both urban and rural samples were included. The term of the study was 1 day only, and all patients who visited the participating physicians on the study day were enrolled in the study. The physicians explained the purpose of the study and written informed consents were obtained from the patients. This study was approved by the Ethics Committee of Tohoku University School of Medicine (approval number 2001-223). The number of subjects necessary to enroll was estimated according to the theory of experimental design. Taking into account that the prevalence of IBS at a hospital department of gastroenterology in the United Kingdom is 30%,⁴ a sample size of over 400 subjects was enough for data analysis.

Questionnaire

RIIMQ, Respondent Form

This self-administered questionnaire for IBS diagnosis is based on the Rome II criteria.¹⁸ Reliability and validity of both the English and Japanese versions of RIIMQ had already been established.^{19,22} The questionnaire is composed of 4 crucial questions and 11 additional questions. The 4 crucial questions determine whether the patient has IBS or not. The 11 additional questions are about supporting symptoms and they are used to determine subgroups of IBS. The subgroups are classified as constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), and others classified neither

IBS-C nor IBS-D (alternating, IBS-A). The Japanese version of RIIMQ can be provided by the corresponding author.

In this survey, patients who reported no bowel symptoms were classified as normal and patients who had signs of bowel symptoms but did not satisfy Rome II criteria were regarded as having functional bowel disorder (FBD).

Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ)

This modified version of the self-reported IBS symptom evaluation scale consisting of a total of 21 items was prepared at Tohoku University.²³ SIBSQ is based on the Rome II criteria, and its Japanese version has already been validated.²² The subjects answered 14 questions about their GI symptoms and 7 questions about the characteristics and number of stools, the presence or absence of stress, and the frequency of hospital visitations during a period of 1 week in their daily lives. Regarding GI symptoms, the questions included abdominal pain, abdominal discomfort, frequency of defecation, characteristics of stools (2 questions), feeling of residual stools, feeling of abdominal distention, bloating, feeling of incomplete evacuation, straining during defecation, anxiety for abdominal pain, relation between stress and bowel symptoms, and the relation between meals and bowel symptoms. Answers to SIBSQ were rated by Likert's scale from 1 (nothing at all) to 7 (extremely present), and the sum of the 14 questions about GI symptoms was taken as IBS score, which reflects the severity of IBS in Japan.²³ The other 7 questions had 7 options grading the frequency or severity by frequency, and the subjects were asked to select one option among them.

Demographic Data

The following 10 items were investigated: (1) sex, (2) age, (3) occupation, (4) smoking, (5) alcohol, (6) diet, (7) sleeping, (8) perceived stress, (9) analysis of medical visits, and (10) name of the disease or condition the patient was diagnosed with during past visits. Demographic items were shown in Table 1.

Methods

After receiving patients' informed consents, the physicians handed the questionnaires to the patients who completed them during their waiting time. Diagnoses of each patient's past visits were recorded by the physician. Clinical diagnosis of IBS was made by the physicians based on Rome II criteria or on each physician own criteria, including complete blood counts, blood chemical examination, plasma inflammatory response, fecal occult blood, and colon-fiberscopy or Ba enema and flexible sigmoidoscopy if necessary. Diagnosis for other diseases was made by accurate clinical examinations.

Statistical Analysis

SPSS 11.0J for Windows was used for statistical analysis. Analysis of variance (ANOVA), χ^2 test, and the Kruskal-Wallis test were performed to evaluate differences

TABLE 1. Demographic Data

Items	Unit	Male	Female	Total
Sex	%	305 (48.2)	328 (51.8)	633 (100.0)
Age	yo/range	16-96	15-93	15-96
	yo/mean \pm SD	57.1 \pm 16.3	58.3 \pm 20.1	57.6 \pm 18.4
Occupation				
Full-time	n (%)	139 (22.0)	62 (9.8)	201 (31.8)
Part-time	n (%)	22 (3.5)	51 (8.1)	73 (11.5)
Retire	n (%)	64 (10.1)	19 (3.0)	83 (13.1)
No occupation, layoff	n (%)	49 (7.7)	46 (7.3)	95 (15.0)
Homemaker	n (%)	4 (0.6)	118 (18.6)	122 (19.3)
Student	n (%)	5 (0.8)	12 (1.9)	17 (2.7)
Others	n (%)	22 (3.5)	20 (3.2)	42 (6.6)
Smoking				
No	n (%)	188 (29.7)	276 (43.6)	464 (73.3)
Yes	n (%)	117 (18.5)	52 (8.2)	169 (26.7)
Cigarette/d	d/mean \pm SD	20.6 \pm 10.6	15.9 \pm 9.3	19.2 \pm 10.8
Alcohol				
No	n (%)	124 (19.6)	214 (33.8)	338 (53.4)
Drink sometimes	n (%)	80 (12.6)	87 (13.7)	167 (26.4)
Drink everyday	n (%)	101 (16.0)	27 (4.3)	128 (20.2)
Diet				
Always regular	n (%)	93 (14.7)	144 (22.7)	237 (37.4)
Sometimes irregular	n (%)	161 (25.4)	153 (24.2)	314 (49.6)
Always irregular	n (%)	51 (8.1)	31 (4.9)	82 (13.1)
Sleeping				
Always regular	n (%)	93 (14.7)	144 (22.7)	237 (37.4)
Sometimes irregular	n (%)	170 (26.9)	169 (26.7)	339 (53.6)
Always irregular	n (%)	55 (8.7)	59 (9.3)	114 (18.0)
Perceived stress				
No	n (%)	200 (31.6)	190 (30.0)	390 (61.6)
Yes	n (%)	105 (16.9)	138 (21.8)	243 (38.4)
Initial visit				
No	n (%)	45 (7.1)	152 (24.0)	197 (31.1)
Yes	n (%)	260 (41.1)	176 (27.8)	436 (68.4)
Cause of consultation				
Hypertension	n	50	57	107
Diabetes	n	60	46	106
Peptic ulcer	n	47	15	62
IBD	n	22	36	58
Hepatitis/cirrhosis	n	23	19	42
Pancreatitis	n	13	19	32
Insomnia	n	5	10	15
Angina pectoris	n	8	6	14
Gallstone	n	2	7	9
Others	n	18	52	70

IBD indicates inflammatory bowel disease; SD, standard deviation; yo, years old.

among the study subjects. Statistical significance was regarded at P value less than 0.05.

RESULTS

Answers to the study questionnaires were obtained from 1045 patients. Seven hundred ninety-one patients (75%) completely answered the RIIMQ, 639 (61%) patients completely answered the SIBSQ, and 689 (66%) patients answered the demographic questionnaire. Of the 1045 patients, 633 patients (61%) completely answered all of the questionnaires. The demographic data of 633 patients are shown in Table 1. The patients were aged 57.6 ± 18.4 , with 305 males and 328 females, 68.4% of the patients visited the hospital initially, and the causes

of their visits were common diseases related to internal medicine. Of those patients, 196 (31%) were diagnosed as having IBS (Fig. 1). The prevalence of IBS among females (34.1%) tended to be more than that among males (27.5%, χ^2 value = 2.92, $P < 0.1$, Fig. 1). Two hundred seventy-six patients (44%) were diagnosed as having FBD and 161 patients (25%) were classified as normal. There was no significant difference in the prevalence of FBD between males and females.

ANOVA revealed a significant difference in IBS scores of SIBSQ among IBS subjects (39.0 ± 11.1 , mean \pm standard deviation), FBD subjects (27.1 ± 10.2) and normal subjects (24.0 ± 10.0 , $P < 0.01$, Fig. 2). A post hoc test confirmed that IBS scores in IBS subjects were significantly higher than those in normal subjects

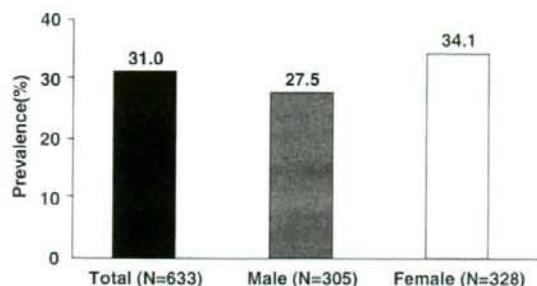


FIGURE 1. Sex difference in the prevalence of IBS among outpatients in Japan. The prevalence of IBS in medical outpatients denoted 31% in Japan. The prevalence of IBS in females tended to be more than that in males ($\chi^2=2.92$, $P<0.1$).

($P < 0.01$) or FBD subjects ($P < 0.01$). IBS scores in FBD subjects were significantly higher than those in normal subjects ($P < 0.01$).

Table 2 shows the subgroups of IBS subjects: 42 subjects (21.4%) were IBS-C, 58 subjects (29.6%) were IBS-D, and 96 subjects (49.0%) were IBS-A. The sex ratio (male:female) of the subgroups was as follows: IBS-C (1:1), IBS-D (1:1.52), and IBS-A (1:1.4, Table 2). There was no significant difference in the sex ratio among IBS subgroups.

The prevalence of IBS depending on age is shown in Figure 3. The ages of the subjects ranged from 15 to 96 years old. The proportion of the population depending on age in this study was not significantly different from the proportion of the total population of Japan depending on age given in September 2002 by the Ministry of Health, Labour and Welfare of Japan. The prevalence of IBS

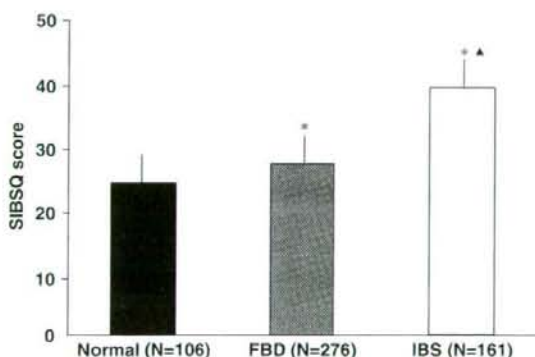


FIGURE 2. The SIBSQ scores of patients with IBS, those with FBD, and normal subjects. A significant difference among the 3 groups of subjects was detected by ANOVA ($F=17$, $P<0.01$). Post hoc test revealed significant difference between normal subjects and subjects with FBD ($P<0.01$), normal subjects and subjects with IBS ($P<0.01$), and subjects with FBD and those with IBS ($\blacktriangle P<0.01$).

TABLE 2. IBS Subgroups

	Male (%)	Female (%)	Total
IBS-C	21 (10.7)	21 (10.7)	42 (21.4)
IBS-D	23 (11.7)	35 (17.9)	58 (29.6)
IBS-A	40 (20.4)	56 (28.6)	96 (49.0)
Total	84 (42.8)	112 (57.2)	196 (100)

was relatively high (43% to 56%) among the 10 to 30-year olds, but gradually declined age-dependency and formed a nadir (14%) in patients in their 70-years-old. After 70-years-old, the prevalence of IBS gradually increased again. These changes in the prevalence of IBS were statistically significant ($\chi^2_8 = 20.8$, $P < 0.05$). IBS symptoms in the elderly were independent on the organic comorbidity.

Figure 4 shows the ratio of RIIMQ-defined IBS or FBD among the top 6 common medical diseases in Japanese outpatients. A significantly different distribution of IBS or FBD status was observed among physician-diagnosed medical diseases (ANOVA, $P = 0.01$). The prevalence of subjects with RIIMQ-defined IBS (72%) was significantly high among physician-diagnosed IBS patients ($P < 0.01$). In the other 5 medical diseases, the prevalence of IBS ranged from 12% to 33%. The prevalence of IBS in the remaining various diseases denoted 44%.

Table 3 shows differences in perceived stress, lifestyle, and hospital visiting status among IBS, FBD, and normal subjects. Perceived stress ($P < 0.0001$), meal habits ($P < 0.0001$), and sleep habits ($P < 0.0001$) significantly differed among the 3 groups. IBS patients had significantly more perceived stress, less regular sleep, and meal habits. There was no difference in smoking and drinking behavior or in hospital visiting status among the 3 groups.

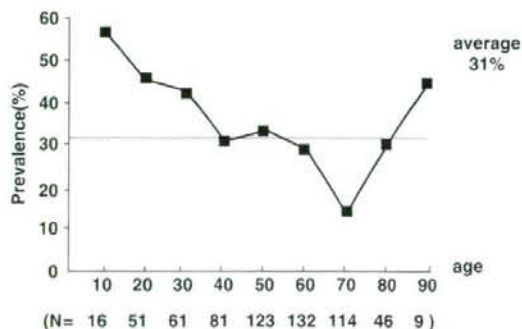


FIGURE 3. The age distribution in the prevalence of IBS among medical outpatients. Changes in prevalence of IBS depending on age were statistically significant ($\chi^2=20.8$, $P<0.05$).

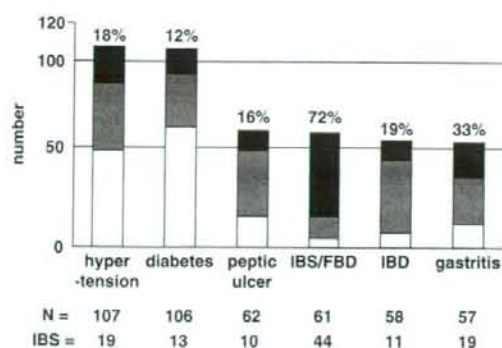


FIGURE 4. Physician's diagnosis and IBS/FBD status. Significantly different distribution of IBS/FBD status was observed among the physician-diagnosed medical diseases (ANOVA, $F=11$, $P<0.01$). RIIMQ-defined IBS was significantly higher in IBS/FBD patients ($P<0.01$). Boxes are indicated as follows: closed box ■; IBS, shaded box ▒; FBD, and open box □; normal.

DISCUSSION

This study is the first national survey of the prevalence of Rome II-defined IBS among medical outpatients in Japan. RIIMQ correctly reflected the validated IBS scores of SIBSQ. In addition, subjects diagnosis based on RIIMQ correctly reflected physician-diagnosed IBS status. Because RIIMQ is available in English-speaking countries,^{18,19} the results of this study are comparable with those obtained in those countries.

In this study, the prevalence of IBS in Japanese medical outpatients was 31%. This value is as high as the 30% prevalence of IBS obtained in the United Kingdom.⁴

TABLE 3. Stress/Life/Style and IBS/FBD Status

Items	Choices	Normal (N = 161, %)	FBD (N = 276, %)	IBS (N = 196, %)
Smoking	Yes	26.0	71.7	25.0
	No	73.9	28.2	75.0
Alcohol	No	53.0	50.7	58.6
	Drink	26.7	27.5	24.5
	sometimes			
	Drink	19.9	21.7	18.4
Diet*†	Regular	42.8	38.7	31.9
	Sometimes	50.3	51.8	45.9
	irregular			
	Irregular	6.8	9.4	23.0
Sleeping*†	Regular	29.8	32.9	71.0
	Sometimes	59.0	53.3	49.5
	irregular			
	Irregular	11.2	3.6	29.6
Perceived stress*†	Present	29.2	31.9	55.1
	Absent	70.8	68.1	44.9
Initial visit	Yes	85.7	88.4	85.7
	No	14.3	11.6	14.3

*Compared with normal vs. IBS, $P < 0.0001$.

†Compared with FBD vs. IBS, $P < 0.0001$.

However, the study conducted in the United Kingdom included only patients with GI complaints. It is striking that 31% of Japanese patients who visited hospitals departments of internal medicine during our study were diagnosed with IBS even if the sample patients were not restricted to GI diseases. The rationale for the high prevalence of IBS in medical outpatients in Japan may be the influence of the rapidly increasing westernized eating habits, irregular sleeping habits, and the stressful social life in Japan. Indeed, previous studies have shown that Japanese who have low fiber intake have more GI complaints,²⁴ increased sleep disorders,²⁵ and increased psychosocial stress,²⁶ all of which are associated with IBS.^{13,27-28}

Most epidemiologic data of IBS from western countries show that IBS is dominant in females.¹⁻⁵ This study also denoted a trend of female dominance. However, an earlier epidemiologic survey in Japan reported that males had a higher prevalence of Rome I-defined IBS than females.²¹ As the earlier survey²¹ did not use a validated questionnaire for IBS, our study here seems to be close to accurate IBS status in Japan. In addition, the lack of a stronger dominance among females in Japanese IBS subjects may be due to the somewhat weaker sex effect than those in western countries.

In our paper, IBS-A is the remaining IBS other than IBS-C or IBS-D. In the systematic review of bowel habit subtypes of IBS,²⁹ primary care office-based studies showed IBS-A as the most prevalent group such as 52.4% or so. The prevalence 49% of IBS-A in our study is comparable data with the earlier reports.²⁹

The prevalence of IBS depending on age in this study showed results similar to those in the United States and Europe^{30,31} even though the age range was slightly higher in this study. The highest prevalence of IBS was obtained among teenagers, then the prevalence decreased with age until the 70s. The prevalence of IBS in the 90s was also high, second only to teenagers. However, the small number of subjects (4 in 9 subjects) was not enough to draw a firm conclusion. On the other hand, when calculating the proportion of people aged 85 years and above to the total Japanese population in accordance with the estimated national population classified by sex and age in September 2002, it is only 2%, which is the same ratio as in this study. In addition, an earlier study has suggested that the prevalence of IBS increases with increased age.³² Therefore, worldwide prevalence of IBS depending on age may form 2 peaks, first among adolescents and second among the elderly. Although data of high prevalence of IBS in the elderly should be considered carefully, independence of IBS comorbidity with the organic diseases in the elderly suggest the aging over 70 as a potential risk of IBS. Larger survey focusing IBS and the elderly is necessary.

The high (72%) but not maximal (100%) prevalence of RIIMQ-defined IBS-D in physician-diagnosed IBS or FBD is not surprising, because general physicians do not always agree to use Rome II criteria.²² The prevalence of IBS in patients with various medical diseases (44%)

or gastritis (33%) was also very high. In addition, a considerable prevalence of IBS in patients with hypertension (18%) or diabetes mellitus (12%) was detected. These findings suggest that IBS is a hidden medical problem among patients who visit hospitals departments of internal medicine.

Similar to earlier reports,^{12,13} this study proved a higher perception of psychosocial stress in patients with IBS. Although earlier reports have also suggested a hypersensitivity to food in IBS patients,^{33,34} this study clarified that long-term irregular dietary and sleeping behavior among IBS patients plays a role in the pathogenesis of IBS. Actually, the therapeutic guideline for IBS in the United Kingdom focuses on modification of life style.²⁷ Whether only behavioral modification, such as stress inoculation, a regular diet and/or regular sleep cycles, may improve the status of IBS is a testable hypothesis.

The sample size (633) of this study is considered to be enough to estimate the prevalence of IBS in outpatients in Japan. It is much more than the number (400) indicated by the theory of sample size determination and the number of subjects (255) published in an earlier study conducted in the United Kingdom.⁴ In addition, the response rate (60.6%) in our study was much more higher than that in the earlier report,⁴ and the surveyed area covered all districts of Japan. Finally, the number of outpatients consultation during the study was close to the average number of daily practice in Japan.

There are several limitations to this study. First, the patients were enrolled at outpatient departments of internal medicine that belong to the IBS Club. Therefore, the data obtained from the study might be biased by patients who knew physicians' interest in IBS. Second, the collective ratio of subjects who completely responded to the questionnaires was only 61%. However, this ratio was similar to those reported in earlier studies (approximately 60% of total sample).^{19,35,36} Therefore, it is possible to compare the results of this study with those of previous studies. Third, we could not discriminate whether IBS symptoms were due to organic GI disorder per se. Further investigation on organic GI symptoms is necessary.

CONCLUSIONS

In this study, we conducted the first national survey of the prevalence of Rome II-defined IBS among outpatients in Japan. We found that the prevalence of IBS in medical outpatients in Japan is 31%. Perceived stress together with irregular dietary and sleeping behavior are suggested to be the main causes of this high prevalence of IBS among medical outpatients in Japan.

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Corticotropin-releasing hormone receptor 1 antagonist blocks colonic hypersensitivity induced by a combination of inflammation and repetitive colorectal distension

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Abstract Gastroenteritis is one of the risk factors for developing irritable bowel syndrome (IBS). However, the precise mechanism of postinfectious IBS is still unknown. We tested the hypothesis that a combination of previous inflammation and repetitive colorectal distention (CRD) makes the colon hypersensitive and that treatment with a corticotropin-releasing hormone receptor 1 (CRH-R1) antagonist blocks this colonic hypersensitivity. Rats were pretreated with vehicle or 2,4,6-trinitrobenzene sulphonic acid (TNBS) 6 weeks before CRD. For the CRD experiment, the colon was distended once a day for six consecutive days. The CRH-R1 antagonist (CP-154,526, 20 mg kg⁻¹) or vehicle was injected subcutaneously 30 min before CRD. Visceral perception was quantified as visceromotor response (VMR) using an electromyograph. For histological examination, the rats were killed on the last day of CRD experiment, and haematoxylin and eosin-staining of colon segments was performed. Although from the first to the third day of CRD, VMRs increased in both the vehicle-treated rats and TNBS-treated rats, they were significantly higher in TNBS-treated rats than those in vehicle-treated controls. On the fifth day of CRD, however, VMRs in the vehicle-treated rats were significantly greater than those in TNBS-treated rats. Pretreatment of rats with CP-154,526 significantly attenuated the increase in VMR induced by repetitive CRD with previous inflammation. Finally, we found that repetitive CRD and repetitive CRD after colitis induced visceral inflammation. These results indicate that a combi-

nation of previous inflammation and repetitive CRD induces visceral hypersensitivity and that a CRH-R1 antagonist attenuates this response in rats.

Keywords corticotropin-releasing hormone receptor 1, inflammation, repetitive colorectal distension, sensitization, visceral hypersensitivity.

Abbreviations: CRD, colorectal distention; CRH-R1, corticotropin-releasing hormone receptor 1; EMG, electromyographic; GABA, γ -amino butyric acid; IBS, irritable bowel syndrome; PI-IBS, postinfectious IBS; TNBS, 2,4,6-trinitrobenzene sulphonic acid; VMR, visceromotor response.

INTRODUCTION

Irritable bowel syndrome (IBS), a prototypic functional gastrointestinal disorder,^{1,2} is generally accompanied by hypersensitivity to rectal^{3,4}/colonic⁵ distention and increased intestinal reactivity to psychosocial stressors.^{6–8} Because IBS has an estimated prevalence of 3–22% of the population,^{9–11} it is believed that common life events account for the sensitization process in IBS patients. Several prospective studies have indicated that a substantial proportion of patients (7–33%) with acute bacterial gastroenteritis develop IBS symptoms that persist for many months.^{12–14} Although there are many possible causes of IBS, two prospective studies using non-infected controls have indicated that bacterial gastroenteritis is one of the main risk factors for developing IBS, which is known in this case as postinfectious IBS (PI-IBS).^{15,16} Moreover, individual susceptibility to psychosocial stressors, such as depression, anxiety and somatization, before acute gastroenteritis is a strong predictor of PI-IBS.^{12,13,16}

Various types of stress are known to increase parameters associated with colonic inflammation. For instance, acute cold-restraint stress and water-avoidance stress have been shown to enhance ionic and

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macromolecular permeability.^{17,18} In addition, chronic water-avoidance stress has been reported to induce barrier dysfunction, bacterial adhesion and penetration into enterocytes, and hyperplasia and activation of mast cells.^{19–21} Moreover, a previous study has indicated that previous colitis makes the colon more vulnerable to stress.²² Indeed, 6 weeks after 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis, restraint stress caused a significant increase in myeloperoxidase activity in TNBS-treated rats but not in the stressed controls.²² Other studies have shown that chronic water-avoidance stress and wrap-restraint stress aggravate TNBS-induced colitis²³ and that acute or previous inflammation induces colon hypersensitive to colorectal distention (CRD).^{24–27} These animal observations are consistent with some of the main symptoms displayed by IBS patients and suggest that rats with previous TNBS-induced colitis can be used as a model of PI-IBS.

Recent advances in neuroscience have clearly conceptualized the idea that information from visceral organs is fundamental for understanding emotional processing.²⁸ In this concept, CRD has been considered as a unique stressor that triggers interoceptive stress response.²⁹ Although corticotropin-releasing hormone (CRH) and its receptor 1 (CRH-R1) are known to play an important role in colonic response to acute stress^{30–34} and in visceral inflammatory responses,^{17,18} little is known about the role of CRH-R1 in the response to repetitive CRD. We have previously reported that chronic CRD induces increased fecal pellet output in response to novel environment stressor in rats.³⁵ This response was not accompanied by elevation of plasma adrenocorticotrophic hormone release and anxiety, but interestingly was blocked by a CRH-R1 antagonist.³⁵ Based on these findings, we wished to examine the effects of a combination of previous inflammation and repetitive CRD on visceral perception and the role of CRH-R1 in the ensuing responses. In this study, we tested the hypothesis that combination of previous inflammation and repetitive CRD makes the colon hypersensitive and that pretreatment with a CRH-R1 antagonist blocks this colonic hypersensitivity. We also tested the hypothesis that the sensitization pattern varies among the days of repetitive CRD.

MATERIALS AND METHODS

Animals

Male Wistar rats ($n = 24$) weighing 180–210 g were purchased from Charles River Breeding Laboratories

Inc. (Yokohama, Japan). The rats were housed under controlled illumination (12 : 12-h light/dark-cycle starting 8:00 AM) and temperature (23 ± 1 °C) with free access to food and water. This study was approved by the Ethics Committee of Laboratory Animals, Tohoku University.

Drugs

The specific CRH-R1 antagonist CP-154,526 (*N*-butyl-*N*-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidin-4-yl]-*N*-ethylamine; Pfizer, Croton, CT, USA) was kept at room temperature and dissolved in a mixture of 5% dimethyl sulphoxide (DMSO; Sigma Chemical Co., St Louis, MO, USA), 5% cremophor El (Sigma) and 90% saline.

Induction of colitis

Induction of colitis and recovery from it were performed as described elsewhere.^{22,23} In brief, rats were lightly anaesthetized with ether, and a medical-grade polyurethane cannula for enteral feeding (external diameter 2 mm) was inserted into the anus and its tip was advanced to 8 cm proximal to the anus verge. 2,4,6-Trinitrobenzene sulphonic acid dissolved in 50% ethanol was instilled into the colon through the cannula (30 mg in a volume of 0.25 mL). Following TNBS instillation, the animals were maintained in a head-down position for a few minutes to prevent leakage of the intracolonic instillate. Control rats were instilled with 0.25 mL of 50% ethanol instead of TNBS/ethanol. After induction of colitis, rats were allowed to recuperate for 6 weeks before testing.

Surgical procedure

Rats were deeply anaesthetized with pentobarbital sodium (50 mg kg⁻¹) administered intraperitoneally. The electrodes of an electromyograph (EMG; Star Medical, Tokyo, Japan) were then stitched into the external oblique musculature for electromyogram recording. Electrode leads were tunneled subcutaneously and exteriorized at the nape of the neck for future access. After surgery, rats were housed individually and allowed to recuperate for 6 days before testing.

Colorectal distention

For CRD, rats were restrained in a tube cage 3 min before EMG recording. A 7- to 8-cm-long polyethylene bag was inserted into the colorectum through the anus, and anchored by taping the balloon catheter to the base

of the tail. The pressure was monitored and kept constant by a pressure controller-timing device (Distender Series II; G & J Electronics, Toronto, ON, Canada). Rats were distended with noxious phasic CRD (80 mmHg, 20 s, 1-min interstimulus interval, 15 times), and their response was quantified as visceromotor response (VMR) characterized by contraction of the abdominal and hindlimb musculature. Electromyographic activity produced by contraction of the external oblique musculature was quantified by recording the number of discharges crossing a preset voltage threshold (baseline), as described previously.³⁶ The preset voltage threshold was determined by data collected 20 s before each distention. EMG recordings were collected and analysed using 8 STAR version 6.0–19.2 for Windows software (Star Medical). An increase in the total number of counts during distention over baseline was taken as response.

Experimental protocol

Repetitive CRD experiments, in which the colorectum of each rat was distended once a day for six consecutive days, started 6 weeks after instillation of TNBS or vehicle. The rats were divided into three groups; repetitive distention alone ($n = 7$), repetitive distention after colitis ($n = 5$), and repetitive distention after colitis and treatment with CRH-R1 antagonist ($n = 7$) (Fig. 1). CRH-R1 antagonist (CP-154,526, 20 mg kg⁻¹) or vehicle was injected subcutaneously 30 min before CRD. For histological examination, the rats were killed on the last day of CRD experiment and colonic segments were obtained from the distal colon (7–8 cm from the anus). Non-stressed rats ($n = 5$), kept under the same housing conditions as the stressed rats, were used as control.

Histological examination

A 1-cm-long piece of the colon was fixed in 10% formalin neutral buffer solution for at least 24 h, embedded in paraffin, and haematoxylin and eosin (H&E)-stained. Tissues from five to seven rats per group were scrutinized, one tissue section per rat, and, for each tissue, 10 contiguous non-overlapping areas above the muscularis mucosae were examined. Neutrophils, eosinophils and intraepithelial lymphocytes were identified, and cells in coded sections were counted and expressed as number of cells per mm² or number of cells per 100 cells.

Statistical analysis

All data are expressed as the mean \pm standard error (SE). Mean value of the initial three (first, second and third) recordings on the first day was set as 100% VMR. Each datum was calculated as percentage VMR. Percentage VMR to each stimulus was first analysed and then the mean value for each day was calculated. Statistical significance was evaluated using ANOVA (one- and 2-way, repeated measures) and the *post hoc* test. A probability level of 0.05 or less was considered to be statistically significant.

RESULTS

Effects of previous inflammation on repetitive colorectal distention-induced visceromotor response

Significant period effect ($F = 3.5$, $P < 0.001$) and group \times period interaction ($F = 4.7$, $P < 0.001$) were detected by two-way ANOVA on percentage VMR

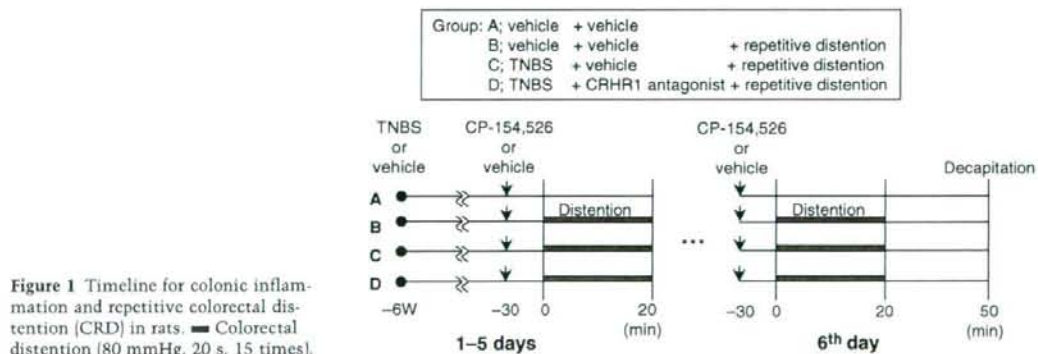


Figure 1 Timeline for colonic inflammation and repetitive colorectal distention (CRD) in rats. ■ Colorectal distention (80 mmHg, 20 s, 15 times).