Life-event stress induced by the Great East Japan Earthquake caused relapse in ulcerative colitis but not in Crohn's disease: a retrospective cohort study

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Original research article: Life-event stress induced by the Great East Japan Earthquake caused relapse in ulcerative colitis but not in Crohn's disease: a retrospective cohort study

Short title: Relapse of Ulcerative colitis by the Great East Japan Earthquake

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Abstract

Objective: Stress is thought to be one of the triggers of flares in patients with inflammatory bowel disease (IBD). We examined the rate of relapse in IBD patients before and after the Great East Japan Earthquake.

Design: A retrospective cohort study.

Settings: 13 hospitals in Japan.

Participants: 546 ulcerative colitis (UC) and 357 Crohn's disease (CD) patients who received outpatient and inpatient care at 13 hospitals located in the area which suffered serious damage from the Earthquake. Data on patient's clinical characteristics, disease activity and deleterious effects of the Earthquake were obtained from questionnaires and hospital records.

Primary outcome: We evaluated the relapse rate (from inactive to active) across two consecutive months before and two consecutive months after the Earthquake, respectively. In this study, we defined "active" as conditions with a partial Mayo score = 2 or more (UC) or a Harvey-Bradshaw index = 6 or more (CD).

Results: Among the UC patients, disease was active in 167 patients and inactive in 379 patients before the Earthquake. After the Earthquake, activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed (relapse rate = 15.8 %). The relapse rate was about twice that of the corresponding period in the previous year. Among the CD patients, 86 patients had active

disease and 271 had inactive disease before the Earthquake. After the Earthquake, activity indices changed little. A total of 25 patients experienced relapse (relapse rate = 7.0 %). The relapse rate did not differ from that of the corresponding period in the previous year. Multivariate analyses revealed that UC, changes in dietary oral intake and anxiety about the family finances were associated with the relapse.

Conclusion: Life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD.

(294 words)

Keywords

earthquake, ulcerative colitis, Crohn's disease, relapse

Article summary

Article focus

Stress is thought to be one of the triggers of flares in patients with inflammatory bowel disease (IBD); however, it is not ethical to impose stressful circumstances on IBD patients in order to examine their effects.

Disease onset or aggravation of cardiovascular disease, respiratory disease, peptic ulcer, etc. was reported to increase after the huge earthquake; however, there has been no report about flares of IBD caused by the huge earthquake.

Key messages

We examined the rate of relapse in IBD patients before and after the huge earthquake, the Great East Japan Earthquake of 11 March 2011 in Japan.

Life-event stress induced by the Earthquake caused relapse in ulcerative colitis (UC) but not in Crohn's disease.

This report indicates that we should take care of stress in the management of patients with IBD, especially with UC.

Strengths and limitations of this study

This is the first report that investigated activities of a large number of IBD patients before and after the huge earthquake.

We did not use validated scores that would objectively assess psychological stress, because it is impossible to investigate stress several times before and after an unexpected earthquake.

Our study cannot disregard recall bias.

Introduction

Inflammatory bowel disease (IBD) is a chronic remitting/relapsing disease. No variable has been defined to be a trigger of flares in patients with IBD. Stress has been indicated as one possible trigger of flares. [1 2 3 4 5 6 7 8] On the other hand, some reports did not prove a relationship between psychological stress and flares of IBD. [9 10 11] A prospective or well-established case-controlled study should be undertaken to determine whether stress is actually related to flares of IBD; however, it is morally difficult to impose stressful circumstances on IBD patients in order to examine their effects.

On 11 March 2011, Japan was hit by one of the most powerful earthquakes in recorded history, the Great East Japan Earthquake. The disaster left more than 28,000 people dead or missing, caused great damage or hardship in dairy life, and also caused profound stress for all of the people, even those who did not suffer individual losses. It was surely one of the most stressful life events and might contribute to relapse in IBD patients. In terms of earthquake-induced disease onset or aggravation, cardiovascular disease, respiratory disease, diabetes mellitus, hypertension and peptic ulcer were reported to increase after the huge earthquake. [12 13 14 15 16 17] However, there has been no report about flares of IBD caused by the huge earthquake.

In this study, we examined activities of IBD patients before and after the Great East Japan

Earthquake, to evaluate the relapse rate and the remission rate induced by the Earthquake. We also aimed to identify factors that were related to relapse or remission of IBD.

Materials and methods

Study subjects

Thirteen hospitals (Tohoku University Hospital, Japanese Red Cross Ishinomaki Hospital, Sendai Medical Center, Takagi Clinic, Osaki Citizen Hospital, Sendai City Hospital, Japanese Red Cross Sendai Hospital, Miyagi Cancer Center, South Miyagi Medical Center and Kesennuma City Hospital in Miyagi Prefecture; Iwate Prefectural Isawa Hospital, Iwate Prefectural Chubu Hospital, Iwate Prefectural Iwai Hospital in Iwate Prefecture) participated in this study. These hospitals are located in the area that suffered serious damage from the Great East Japan Earthquake. We sent questionnaires to ulcerative colitis (UC) and Crohn's disease (CD) patients who received care in these hospitals. Then we examined the hospital records for data on the patients who returned a questionnaire. Hospital data contained information such as gender, age, IBD duration, disease extent (total colitis, left-sided colitis and proctitis in UC), disease location (small intestine, colon and both in CD), extra-intestinal complications, use of medications, smoking status, and pregnancy experience. To evaluate the degree of stress objectively, we also obtained data about each patient's situation regarding the Earthquake, such as damage to the patient's house, duration of temporarily homelessness, deaths of family member or friends, changes in daily dietary intake, discontinuation or delay in taking medications, loss of job, family finances and changes in smoking status. We divided housing

damage into 4 groups according to the degree of damage to the house; total loss (≥50%), half-loss (≥20% but <50%), partial loss (≥3% but <20%) and no damage. Written informed consent was obtained from all participants under the protocol approved by the Tohoku University Hospital Committee for Clinical Investigation.

We evaluated disease activity for two consecutive months before and two consecutive months after the Great East Japan Earthquake using Mayo score for UC [18] or Harvey-Bradshaw index for CD [19] that had been noted in hospital records and questionnaires. The Mayo score is comprised of information on stool frequency, rectal bleeding, findings on endoscopy and a physician's global assessment. Scores can range from 0 to 12. However, we used a partial Mayo score (range from 0 to 9) that excluded findings on endoscopy because routine endoscopic examinations were not performed so soon after the Earthquake. The Harvey-Bradshaw index is comprised of information on general condition, abdominal pain, diarrhea frequency, abdominal mass and complications. Higher scores for both the Mayo score and the Harvey-Bradshaw index indicate more severe disease activity. IBD patients having a stoma were excluded because of difficulties in the count of bowel movements.

In this study, "active" was defined as follows; a partial Mayo score = 2 or more (UC) and a Harvey-Bradshaw index = 6 or more (CD). Lower scores indicated inactive disease. We defined "relapse" as a change from inactive to active and "remission" as a change from active to

inactive across the 2-months before and 2-months after the Earthquake. The patients who remained active or inactive during the study period were considered to have "stable disease". We compared the relapse and remission rates with those during the corresponding period in the previous year as controls.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD). Discrete variables are presented as median and range. All statistical analyses were performed using the JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences between two groups were evaluated using chi-square test or Fisher's exact probability test, unpaired t-test or Wilcoxon signed-rank test, as appropriate. A multiple logistic regression method that included all possible variables was used. The level of statistical significance was set at $P < 0.05$.

Results

Patients' clinical characteristics

A total of 903 completed questionnaires (from 546 UC and 357 CD) were returned to us. We examined the hospital records for each patient. Of the UC patients, 269 (49.3%) were males and 277 (50.7%) were females. The mean age of the entire group was of 45.3 ± 16.6 years and mean disease duration was 9.7 ± 9.0 years. Extent of disease was as follows; 208 patients (38.1%), total colitis (over splenic flexure); 183 (33.5%), left-sided colitis (up to splenic flexure); and 83 (15.2%), proctitis (up to rectum). Extent was unknown in 72 patients (13.2%). Among the CD patients, there were 253 males (70.9%) and 104 females (29.1%). Mean age was 37.1 ± 12.5 years and mean disease duration was 11.6 ± 8.1 years. Location of disease was as follows; 61 patients (17.1%), small intestine; 47 (13.2%), colon; and 212 (59.4%), both small intestine and colon. Location was unknown in 37 patients (10.3%) (Table 1).

Fifty-one UC (9.3%) and 43 CD (12.0%) patients experienced extra-intestinal complications. Of the UC patients, 55 patients (10.1%) were current smokers and 162 (29.7%) were past smokers. On the other hand, 85 CD patients (23.8%) were current smokers, and 74 (20.7%) were past smokers. Of 277 females with UC, 181 (65.3%) had experienced pregnancy while only 41 of 104 CD females (39.4%) had experienced pregnancy. Five UC patients and 3 CD patients were just pregnant when the Earthquake occurred (Table 1). Medications used by the

IBD patients before the Earthquake are shown in Table 2.

Deleterious effects of the Earthquake

Of the 903 IBD patients, the houses of 501 patients (55.5%) were damaged; partial loss was experienced by 369 patients (40.9%), half-loss by 58 (6.4%), and total loss by 74 (8.2%). As a result, 62 (6.9%) patients had to stay in refuge facilities for one week or more. A total of 175 patients (19.4%) experienced the death of a family member or a friend (Table 3).

Only 51 patients (5.7%) experienced complete loss of their jobs after the Earthquake. However, 279 (30.9%) and 157 (17.4%) patients felt short-term (for the next several months) and long-term (for the next several years) anxiety about their family finances, respectively (Table 3).

Because of temporarily homelessness and difficulty in getting the usual foods consumed, changes in daily intake such as fat, vegetables, fruits, etc. were experienced by 269 patients (29.8%) after the Earthquake. With regard to medications, 69 patients (11.7%) interrupted medications for a week or more because they had lost their medicines or could not consult with doctors (see Table 3).

Changes in disease activity before and after the Earthquake

Of the UC patients, disease was active in 167 patients (30.6%) and inactive in 379 patients (69.4%) before the Earthquake. After the Earthquake, activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed and disease status became inactive in 22 patients; therefore the relapse rate (from inactive to active) was 15.8% (86/546) and the remission rate (from active to inactive) was 4.0% (22/546). The relapse rate was significantly higher than in the previous year (8.8%, data not shown). On the other hand, the remission rate was significantly lower than in the previous year (8.8%, data not shown).

Of the CD patients, 86 patients (24.1%) had active disease and 271 patients (75.9%) had inactive disease before the Earthquake. After the Earthquake, activity indices were little changed. A total of 25 patients relapsed and disease status became inactive in 16 patients; therefore the relapse rate (from inactive to active) was 7.0% (25/357) and the remission rate (from active to inactive) was 4.5% (16/357). Unlike in UC, the relapse rate among CD patients was slightly higher than in the previous year (5.3%, data not shown), but not significantly. On the other hand, the remission rate was twice that of the previous year (2.2%, data not shown), but did not differ significantly.

Because of disease flares, 96 patients (10.6%) needed additional medications after the Earthquake as follows: prednisolone (27 patients), tacrolimus (3), azathioprine (11), infliximab (13), adalimumab (6), total parenteral nutrition (4), or others.

Possible variables for relapse or remission

There were no differences in patients' clinical characteristics between the relapse group and non-relapse group. With regard to remission, there were also no differences in patients' clinical characteristics between the remission group and non-remission group.

Multivariate analyses revealed that UC, changes in oral intake and anxiety about the family finances were independent predictors of relapse with an adjusted odds ratio (OR) of 2.86 (95% confidence interval (CI), 1.73 to 4.87), 1.83 (1.16 to 2.88) and 1.69 (1.05 to 2.70), respectively (Table 4). On the other hand, no factor was identified as an independent predictor of remission (Table 5).

Discussion

Of the 903 IBD patients, 132 patients (14.6%) had experienced damage to their houses of half or more and 175 patients (19.4%) experienced the deaths of a family member or friends. These factors confirm that the Great East Japan Earthquake had considerable power and was certainly one of the most stressful life events that could be experienced. The present study showed that life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD. This is the first report that investigated activities of a large number of IBD patients before and after the huge earthquake.

As for patient's clinical characteristics, gender, age, IBD duration, extra-intestinal complications and smoking status did not influence flares of IBD, with the exception of IBD type (UC or CD). As mentioned above, there have been many reports that psychological stress may induce flares of UC. [1 2 3 4 5 6 8] On the other hand, there have been few reports about flares of CD. [4 7 8] Our present study demonstrated that psychological stress caused relapse in UC, but not in CD. Other clinical characteristics, including smoking status, did not induce flares. In terms of damage and other deleterious effects from the Earthquake, damage to houses, duration of temporarily homelessness, death of family members or friends and unemployment did not induce flares of IBD; however, anxiety about family finances was related to relapse. These results may indicate that psychological stress or the uneasiness over the future have a greater

influence on UC flares than direct damage and losses.

Although discontinuation of medications had no influence on flares of IBD, changes in daily dietary intake induced flares. The relation between dietary factors and the onset or flares of IBD has been reported. [20 21 22] After the Earthquake, we could not obtain enough food; therefore we consumed more processed foods and less raw vegetables and fruits. With regard to possible variables for remission, we expected that the decrease in total volume or fatty foods would induce remission, especially in CD patients. However, our results did not consistent with this hypothesis. It may be due to the facts that the period of dietary restriction was not so long, and food rationing began soon. There were just few patients that had changes in smoking status after the Earthquake; therefore we could not include this factor in multivariate analyses. However, changes in smoking status may be an important factor in flares of patients with UC, but not with CD. Of the 9 UC patients who stopped smoking after the Earthquake, 7 experienced relapse (P = 0.002). Beaugerie et al. had reported that among smokers with UC who stopped smoking, disease severity increased after cessation. [23] Over the short term, smoking itself did not have an influence on relapse or remission; however, changes in smoking status caused flares in UC.

Our study had some limitations. First, we did not use validated scores that would objectively assess psychological stress such as the Cohen Perceived Stress Scale. [24] Since a huge earthquake happens suddenly, it is impossible to investigate stress several times before and after an

earthquake. Therefore we assessed the degree of stress by investigating information about damage situations and changes in life styles after the Great East Japan Earthquake. Second, our study cannot disregard recall bias. It was difficult to administer a questionnaire immediately after the Earthquake. That was why we obtained data about clinical characteristics and activities from both questionnaires and medical records. Third, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics may contribute to the relapse of IBD. [25] However, we think the numbers of newly prescribed NSAIDs and antibiotics during the study period were less than or equal to those of the corresponding period in the previous year. Because of the difficulty in obtaining medicines after the Earthquake, the number of newly prescribed NSAIDs and antibiotics might have decreased. In addition, unlike in UC patients, twice as many males as females were among CD patients, which is in agreement with a previous report in Japan. [26] There were more current smokers among CD patients than among those with UC, in agreement with previous reports. [8 20]

Life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD. We hope that this report will help in the usual management of patients with IBD, not only at times of catastrophic events such as a huge earthquake. For the future, a prospective study should be undertaken to determine whether stress is actually related to flares of IBD.

Contributorship statement

Hisashi Shiga and Teruko Miyazawa had the original idea for this study and were involved in writing the original study protocol, data collection and writing manuscript.

Gen Tominaga, Hiroki Takahashi, Sho Takagi, Nobuya Obana, Tatsuya Kikuchi, Shinya Oomori, Eiki Nomura, Manabu Shiraki, Yuichirou Sato, Shuichiro Takahashi, Ken Umemura, Hiroshi Yokoyama, Katsuya Endo, Yoichi Kakuta, Hiroki Aizawa, Masaki Matsuura, Tomoya Kimura and Masatake Kuroha were involved in data collection and contributed to discussion.

Yoshitaka Kinouchi, Seiichi Takahashi and Tooru Shimosegawa contributed to discussion and reviewed manuscript.

All authors had full access to all of the data in this study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

declare that (1) no support from any organaisations for the submitted work; (2) no financial relationships with any organaisations that might have an interest in the submitted work in the previous 3 years; (3) no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was approved by the Tohoku University Hospital Committee for Clinical Investigation. Data are presented in aggregate and no personal health information is disclosed.

Data sharing

No additional data available.

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Tables

Table 1. Patients' clinical characteristics.

		Ulcerative colitis	Crohn's disease	Total
Number of patients		546	357	903
Gender				
Male		269 (49.3%)	253 (70.9%)	522 (57.8%)
Female		277 (50.7%)	104 (29.1%)	381 (42.2%)
Age	year	45.3 ± 16.6	37.1 ± 12.5	42.0 ± 15.6
Disease duration	year	9.7 ± 9.0	11.6 ± 8.1	10.5 ± 8.7
Disease extent				
Total colitis		208 (38.1%)	-	
Left-sided colitis		183 (33.5%)	-	
Proctitis		83 (15.2%)	-	
Unknown		72 (13.2%)	-	
Disease location				
Small intestine		-	61 (17.1%)	
Colon		-	212 (59.4%)	
Small intestine and colon		-	47 (13.2%)	
Unknown		-	37 (10.3%)	
Extra-intestinal complications				
Positive		51 (9.3%)	43 (12.0%)	94 (10.4%)
None		495 (90.7%)	314 (88.0%)	809 (89.6%)
Smoking status				
Current smokers		55 (10.1%)	85 (23.8%)	140 (15.5%)
Past smokers		162 (29.7%)	74 (20.7%)	236 (26.1%)
None		327 (59.9%)	198 (55.5%)	525 (58.2%)
Unclear		2 (0.3%)	0 (0.0%)	2 (0.2%)
Pregnancy experience				
Positive		181/277	41/104	222/381
(During the Earthquake)		(5)	(3)	(8)

Table 2. Use of the medications before the Great East Japan Earthquake.

		Ulcerative colitis (N=546)	Crohn's disease (N=357)	Total (N=903)	
5-ASA or SASP		486 (89.0%)	276 (77.3%)	762 (84.4%)	
PSL		79 (9.0%)	26 (7.3%)	105 (11.6%)	
	(mg)	(1-60)	(1-40)		
AZA or 6-MP		56 (10.3%)	55 (15.4%)	111 (12.3%)	
	(mg)	(15-100)	(10-100)		
Tacrolimus		4 (0.7%)	-	4 (0.4%)	
IFX		18 (3.3%)	151 (42.3%)	169 (1807%)	
	(mg)	(200-500)	(150-500)		
ADA		-	11 (3.1%)	11 (1.2%)	
TPN		0 (0.0%)	3 (0.8%)	3 (0.3%)	
ED			70 (19.6%)	70 (7.8%)	
	(kcal/day)		(300-1,800)		
CAP		3 (0.5%)	1 (0.3%)	4 (0.4%)	

5-ASA, aminosalicilic acid; SASP, salazosurufapirizine; PSL, predonisolone; AZA, azathioprine; MP, mercaptopurine; IFX, infliximab; ADA, adalimumab; TPN, total parenteral nutrition; ED, elemental diet; CAP, cytoapheresis.

Table 3. Damage and deleterious effects of the Great East Japan Earthquake.

	Ulcerative colitis (N=546)	Crohn's disease (N=357)	Total (N=903)
Damage to houses			
Total loss (≥50%)	36 (6.6%)	38 (10.6%)	74 (8.2%)
Half-loss (≥20% but <50%)	37 (6.8%)	21 (5.9%)	58 (6.4%)
Partial loss (≥3% but <20%)	236 (43.2%)	133 (37.3%)	369 (40.9%)
None	233 (42.7%)	161 (45.1%)	394 (43.6%)
Unclear	4 (0.7%)	4 (1.1%)	8 (0.9%)
Temporarily homelessness			
1 week or more	37 (6.8%)	25 (7.0%)	62 (6.9%)
Less than 1 week or none	503 (92.1%)	331 (92.7%)	834 (92.3%)
Unclear	6 (1.1%)	1 (0.3%)	7 (0.8%)
Death of family members or friends			
Yes	106 (19.4%)	69 (19.3%)	175 (19.4%)
None	435 (79.7%)	284 (79.6%)	719 (79.6%)
Unclear	5 (0.9%)	4 (1.1%)	9 (1.0%)
Changes in daily dietary intake			
Yes	153 (28.0%)	116 (32.5%)	269 (29.8%)
No	387 (70.9%)	239 (66.9%)	626 (69.3%)
Unclear	6 (1.1%)	2 (0.6%)	8 (0.9%)
Discontinuation of medications			
1 week or more	39 (9.8%)	30 (14.1%)	69 (11.7%)
None	507 (9.8%)	327 (14.1%)	834 (11.7%)
Unclear	358 (90.2%)	256 (85.9%)	614 (88.3%)
Interruption in IFX or ADA			
Yes	1/18	19/162	20/180
Complete loss of job			
Yes	26 (4.8%)	25 (7.0%)	51 (5.7%)
None	518 (94.9%)	330 (92.4%)	848 (93.9%)
Unclear	2 (0.3%)	2 (5.6%)	4 (0.4%)
Anxiety about family finances			
Yes	167 (30.6%)	145 (40.6%)	312 (34.6%)

(Short-term anxiety)*	(147)	(132)	(279)
(Long-term anxiety)*	(83)	(74)	(157)
None	376 (68.9%)	211 (59.1%)	587 (65.0%)
Unclear	3 (0.5%)	1 (0.3%)	4 (0.4%)
Changes in smoking status			
Stopped after the Earthquake	9	5	14
Restarted after the Earthquake	10	5	15

IFX, infliximab; ADA, Adalimumab. * Short-term anxiety indicates anxiety about their family finances for the next several months. Long-term anxiety indicates anxiety about their family finances several years or more in the future.

Table 4. Possible variables for relapse after the Great East Japan Earthquake.

		Odds ratio	*P* value	95% CI	
IBD type					
Ulcerative colitis	546	2.86	< 0.0001	1.73	4.87
Crohn's disease	357	1			
Gender					
Male	522	0.78	0.26	0.50	1.20
Female	381	1			
Age*					
More than 40 years	423	0.72	0.16	0.45	1.14
40 or less	479	1			
Disease duration					
More than 10 years	350	0.94	0.80	0.58	1.50
10 or less	553	1			
Extra-intestinal complications					
Positive	94	1.40	0.32	0.71	2.59
None	809	1			
Smoking status*					
Current smokers	140	0.95	0.88	0.48	1.76
Others	761	1			
Damage to houses*					
Total or half loss	132	1.01	0.97	0.52	1.88
Others	763	1			
Temporarily homelessness*					
1 week or more	62	0.97	0.94	0.41	2.14
Others	834	1			
Death of family members or friends*					
Yes	175	1.20	0.50	0.70	2.03
None	719	1			
Complete loss of job*					
Yes	51	1.55	0.31	0.65	3.47
None	848	1			
Anxiety about family finances*					

Yes	312	1.69	0.03	1.05	2.70
None	587	1			
Changes in daily dietary intake*					
Yes	269	1.83	< 0.01	1.16	2.88
None	626	1			
Discontinuation of medications					
1 week or more	69	1.49	0.30	0.69	2.98
None	834	1			

CI, Confidence interval. * Information on several patients about age, smoking status, damage to houses, temporarily homelessness, death of family members or friends, complete loss of job, anxiety about family finances, and changes in daily dietary intake was not available.

Table 5. Possible variables for remission after the Great East Japan Earthquake.

		Odds ratio	*P* value	95% CI	
IBD type					
Ulcerative colitis	546	0.81	0.58	0.39	1.72
Crohn's disease	357	1			
Gender					
Male	522	0.84	0.62	0.41	1.72
Female	381	1			
Age*					
More than 40 years	423	0.89	0.76	0.41	1.88
40 or less	479	1			
Disease duration					
More than 10 years	350	0.63	0.25	0.27	1.37
10 or less	553	1			
Extra-intestinal complications					
Positive	94	0.80	0.71	0.19	2.33
None	809	1			
Smoking status*					
Current smokers	140	0.70	0.52	0.20	1.90
Others	761	1			
Damage to houses*					
Total or half loss	132	1.07	0.90	0.33	2.86
Others	763	1			
Temporarily homelessness*					
1 week or more	62	0.82	0.81	0.12	3.40
Others	834	1			
Death of family members or friends*					
Yes	175	0.58	0.28	0.18	1.51
None	719	1			
Complete loss of job*					
Yes	51	2.23	0.28	0.47	7.87
None	848	1			
Anxiety about family finances*					

Yes	312	1.06	0.89	0.47	2.26
None	587	1			
Changes in daily dietary intake*					
Yes	269	1.26	0.55	0.58	2.62
None	626	1			
Discontinuation of medications					
1 week or more	69	0.36	0.26	0.02	1.80
None	834	1			

CI, Confidence interval. * Information on several patients about age, smoking status, damage to houses, temporarily homelessness, death of family members or friends, complete loss of job, anxiety about family finances, and changes in daily dietary intake was not available.

Life-event stress induced by the Great East Japan Earthquake caused relapse in ulcerative colitis but not in Crohn's disease: a retrospective cohort study

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Original research article: Life-event stress induced by the Great East Japan Earthquake caused relapse in ulcerative colitis but not in Crohn's disease: a retrospective cohort study

Short title: Relapse of Ulcerative colitis by the Great East Japan Earthquake

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Abstract

Objective: Stress is thought to be one of the triggers of flares in patients with inflammatory bowel disease (IBD). We examined the rate of relapse in IBD patients before and after the Great East Japan Earthquake.

Design: A retrospective cohort study.

Settings: 13 hospitals in Japan.

Participants: 546 ulcerative colitis (UC) and 357 Crohn's disease (CD) patients who received outpatient and inpatient care at 13 hospitals located in the area which suffered serious damage from the earthquake. Data on patient's clinical characteristics, disease activity and deleterious effects of the earthquake were obtained from questionnaires and hospital records.

Primary outcome: We evaluated the relapse rate (from inactive to active) across two consecutive months before and two consecutive months after the earthquake, respectively. In this study, we defined "active" as conditions with a partial Mayo score = 2 or more (UC) or a Harvey-Bradshaw index = 6 or more (CD).

Results: Among the UC patients, disease was active in 167 patients and inactive in 379 patients before the earthquake. After the earthquake, activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed (relapse rate = 15.8 %). The relapse rate was about twice that of the corresponding period in the previous year. Among the CD patients, 86 patients had active

disease and 271 had inactive disease before the earthquake. After the earthquake, activity indices changed little. A total of 25 patients experienced relapse (relapse rate = 7.0 %). The relapse rate did not differ from that of the corresponding period in the previous year. Multivariate analyses revealed that UC, changes in dietary oral intake and anxiety about the family finances were associated with the relapse.

Conclusion: Life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD.

(294 words)

Keywords

earthquake, ulcerative colitis, Crohn's disease, relapse

Article summary

Article focus

Stress is thought to be one of the triggers of flares in patients with inflammatory bowel disease (IBD); however, it is not ethical to impose stressful circumstances on IBD patients in order to examine their effects.

Disease onset or aggravation of cardiovascular disease, respiratory disease, peptic ulcer, etc. was reported to increase after the huge earthquake; however, there has been no report about flares of IBD caused by the huge earthquake.

Key messages

We examined the rate of relapse in IBD patients before and after the huge earthquake, the Great East Japan Earthquake of 11 March 2011 in Japan.

Life-event stress induced by the earthquake caused relapse in ulcerative colitis (UC) but not in Crohn's disease.

This report indicates that we should take care of stress in the management of patients with IBD, especially with UC.

Strengths and limitations of this study

This is the first report that investigated activities of a large number of IBD patients before and after the huge earthquake.

We did not use validated scores that would objectively assess psychological stress, because it is impossible to investigate stress several times before and after an unexpected earthquake.

Our study cannot disregard recall bias.

Introduction

Inflammatory bowel disease (IBD) is a chronic remitting/relapsing disease. No variable has been proven to be a trigger of flares in patients with IBD. Stress has been indicated as one possible trigger of flares. [1 2 3 4 5 6 7 8] On the other hand, some reports did not prove a relationship between psychological stress and flares of IBD. [9 10 11] A prospective or well-established case-controlled study should be undertaken to determine whether stress is actually related to flares of IBD; however, it is unethical to impose stressful circumstances on IBD patients in order to examine their effects.

On 11 March 2011, Japan was hit by one of the most powerful earthquakes in recorded history, the Great East Japan Earthquake. The disaster left more than 28,000 people dead or missing, caused great damage or hardship in daily life, and also caused profound stress for all of the people, even those who did not suffer individual losses. It was surely one of the most stressful life events and might contribute to relapse in IBD patients. In terms of earthquake-induced disease onset or aggravation, cardiovascular disease, respiratory disease, diabetes mellitus, hypertension and peptic ulcer were reported to increase after the huge earthquake. [12 13 14 15 16 17] However, there has been no report about flares of IBD caused by the huge earthquake.

In this study, we examined activities of IBD patients before and after the Great East Japan Earthquake, to evaluate the relapse rate and the remission rate induced by the earthquake. We also aimed to identify factors that were related to relapse or remission of IBD.

Materials and methods

Study subjects

Thirteen hospitals (Tohoku University Hospital, Japanese Red Cross Ishinomaki Hospital, Sendai Medical Center, Takagi Clinic, Osaki Citizen Hospital, Sendai City Hospital, Japanese Red Cross Sendai Hospital, Miyagi Cancer Center, South Miyagi Medical Center and Kesennuma City Hospital in Miyagi Prefecture; Iwate Prefectural Isawa Hospital, Iwate Prefectural Chubu Hospital, Iwate Prefectural Iwai Hospital in Iwate Prefecture) participated in this study. These hospitals are located in the area that suffered serious damage from the Great East Japan Earthquake. We sent a total of 1,080 questionnaires to ulcerative colitis (UC) and Crohn's disease (CD) patients who received care in these hospitals. Then we examined the hospital records for data on the patients who returned a questionnaire. Hospital data contained information such as gender, age, IBD duration, disease extent (total colitis, left-sided colitis and proctitis in UC), disease location (small intestine, colon and both in CD), extra-intestinal complications, use of medications, smoking status, and pregnancy experience. Written informed consent was obtained from all participants under the protocol approved by the Tohoku University Hospital Committee for Clinical Investigation.

To evaluate the degree of stress objectively, we also obtained data about each patient's situation regarding the earthquake, such as damage to the patient's house, duration of

temporarily homelessness, deaths of family member or friends, changes in daily dietary intake, discontinuation or delay in taking medications, loss of job, family finances and changes in smoking status. We divided housing damage into 4 groups according to the degree of damage to the house; total loss (≥50%), half-loss (≥20% but <50%), partial loss (≥3% but <20%) and no damage.

We evaluated disease activity for two consecutive months before and two consecutive months after the Great East Japan Earthquake using Mayo score for UC [18] or Harvey-Bradshaw index for CD [19] that had been noted in hospital records and questionnaires. The Mayo score is comprised of information on stool frequency, rectal bleeding, findings on endoscopy and a physician's global assessment. Scores can range from 0 to 12. However, we used a partial Mayo score (range from 0 to 9) that excluded findings on endoscopy because routine endoscopic examinations were not performed so soon after the earthquake. The Harvey-Bradshaw index is comprised of information on general condition, abdominal pain, diarrhea frequency, abdominal mass and complications. Higher scores for both the Mayo score and the Harvey-Bradshaw index indicate more severe disease activity. IBD patients having a stoma were excluded because of difficulties in the count of bowel movements.

In this study, "active" was defined as follows; a partial Mayo score = 2 or more (UC) and a Harvey-Bradshaw index = 6 or more (CD). Lower scores indicated inactive disease. We defined

"relapse" as a change from inactive to active and "remission" as a change from active to inactive across the 2-months before and 2-months after the earthquake. The patients who remained active or inactive during the study period were considered to have "stable disease". We compared the relapse and remission rates with those during the corresponding period in the previous year as controls.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD). Discrete variables are presented as median and range. All statistical analyses were performed using the JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences between two groups were evaluated using chi-square test or Fisher's exact probability test, unpaired t-test or Wilcoxon signed-rank test, as appropriate. A multiple logistic regression method that included all possible variables was used. The level of statistical significance was set at $P < 0.05$.

Results

Patients' clinical characteristics

A total of 903 completed questionnaires (from 546 UC and 357 CD) were returned to us. The response rate to the questionnaire was 83.6% (903/1080). We examined the hospital records for each patient. Of the UC patients, 269 (49.3%) were males and 277 (50.7%) were females. The mean age of the entire group was of 45.3 ± 16.6 years and mean disease duration was 9.7 ± 9.0 years. Extent of disease was as follows; 208 patients (38.1%), total colitis (over splenic flexure); 183 (33.5%), left-sided colitis (up to splenic flexure); and 83 (15.2%), proctitis (up to rectum). Extent was unknown in 72 patients (13.2%). Among the CD patients, there were 253 males (70.9%) and 104 females (29.1%). Mean age was 37.1 ± 12.5 years and mean disease duration was 11.6 ± 8.1 years. Location of disease was as follows; 61 patients (17.1%), small intestine; 47 (13.2%), colon; and 212 (59.4%), both small intestine and colon. Location was unknown in 37 patients (10.3%) (Table 1).

Fifty-one UC (9.3%) and 43 CD (12.0%) patients experienced extra-intestinal complications. Of the UC patients, 55 patients (10.1%) were current smokers and 162 (29.7%) were past smokers. On the other hand, 85 CD patients (23.8%) were current smokers, and 74 (20.7%) were past smokers. Of 277 females with UC, 181 (65.3%) had experienced pregnancy while only 41 of 104 CD females (39.4%) had experienced pregnancy. Five UC patients and 3 CD

patients were just pregnant when the earthquake occurred (Table 1). Medications used by the IBD patients before the earthquake are shown in Table 2.

Deleterious effects of the earthquake

Of the 903 IBD patients, the houses of 501 patients (55.5%) were damaged; partial loss was experienced by 369 patients (40.9%), half-loss by 58 (6.4%), and total loss by 74 (8.2%). As a result, 62 (6.9%) patients had to stay in refuge facilities for one week or more. A total of 175 patients (19.4%) experienced the death of a family member or a friend (Table 3).

Only 51 patients (5.7%) experienced complete loss of their jobs after the earthquake. However, 279 (30.9%) and 157 (17.4%) patients felt short-term (for the next several months) and long-term (for the next several years) anxiety about their family finances, respectively (Table 3).

Because of temporarily homelessness and difficulty in getting the usual foods consumed, changes in daily intake such as fat, vegetables, fruits, etc. were experienced by 269 patients (29.8%) after the earthquake. With regard to medications, 69 patients (11.7%) interrupted medications for a week or more because they had lost their medicines or could not consult with doctors (see Table 3).

Changes in disease activity before and after the earthquake

Of the UC patients, disease was active in 167 patients (30.6%) and inactive in 379 patients (69.4%) before the earthquake. After the earthquake, activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed and disease status became inactive in 22 patients; therefore the relapse rate (from inactive to active) was 15.8% (86/546) and the remission rate (from active to inactive) was 4.0% (22/546). The relapse rate was significantly higher than in the previous year (8.8%, data not shown). On the other hand, the remission rate was significantly lower than in the previous year (8.8%, data not shown).

Of the CD patients, 86 patients (24.1%) had active disease and 271 patients (75.9%) had inactive disease before the earthquake. After the earthquake, activity indices were little changed. A total of 25 patients relapsed and disease status became inactive in 16 patients; therefore the relapse rate (from inactive to active) was 7.0% (25/357) and the remission rate (from active to inactive) was 4.5% (16/357). Unlike in UC, the relapse rate among CD patients was slightly higher than in the previous year (5.3%, data not shown), but not significantly. On the other hand, the remission rate was twice that of the previous year (2.2%, data not shown), but did not differ significantly.

Because of disease flares, 96 patients (10.6%) needed additional medications after the earthquake as follows: prednisolone (27 patients), tacrolimus (3), azathioprine (11), infliximab

(13), adalimumab (6), total parenteral nutrition (4), or others.

Possible variables for relapse or remission

There were no differences in patients' clinical characteristics between the relapse group and non-relapse group. With regard to remission, there were also no differences in patients' clinical characteristics between the remission group and non-remission group.

Multivariate analyses revealed that UC, changes in oral intake and anxiety about the family finances were independent predictors of relapse with an adjusted odds ratio (OR) of 2.86 (95% confidence interval (CI), 1.73 to 4.87), 1.83 (1.16 to 2.88) and 1.69 (1.05 to 2.70), respectively (Table 4). On the other hand, no factor was identified as an independent predictor of remission (Table 5).

Discussion

Of the 903 IBD patients, 132 patients (14.6%) had experienced damage to their houses of half or more and 175 patients (19.4%) experienced the deaths of a family member or friends. These factors confirm that the Great East Japan Earthquake had considerable power and was certainly one of the most stressful life events that could be experienced. The response rate to the questionnaire (83.6%) was satisfactory. However, the damage caused by the earthquake might be more serious, because non-response group might include patients who took refuge in somewhere or have died. The present study showed that life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD. This is the first report that investigated activities of a large number of IBD patients before and after the huge earthquake.

As for patient's clinical characteristics, gender, age, IBD duration, extra-intestinal complications and smoking status did not influence flares of IBD, with the exception of IBD type (UC or CD). As mentioned above, there have been many reports that psychological stress may induce flares of UC. [1 2 3 4 5 6 8] On the other hand, there have been few reports about flares of CD. [4 7 8] Our present study demonstrated that psychological stress caused relapse in UC, but not in CD. Other clinical characteristics, including smoking status, did not induce flares. In terms of damage and other deleterious effects from the earthquake, damage to houses, duration of temporarily homelessness, death of family members or friends and unemployment did not

induce flares of IBD; however, anxiety about family finances was related to relapse. These results may indicate that psychological stress or the uneasiness over the future have a greater influence on UC flares than direct damage and losses.

Although discontinuation of medications had no influence on flares of IBD, changes in daily dietary intake induced flares. The relation between dietary factors and the onset or flares of IBD has been reported. [20 21 22] After the earthquake, many patients could not obtain enough food; therefore they consumed more processed foods and less raw vegetables and fruits. With regard to possible variables for remission, we expected that the decrease in total volume or fatty foods would induce remission, especially in CD patients. However, our results did not consistent with this hypothesis. It may be due to the facts that the period of dietary restriction was not so long, and food rationing began soon. There were just few patients that had changes in smoking status after the earthquake; therefore we could not include this factor in multivariate analyses. However, changes in smoking status may be an important factor in flares of patients with UC, but not with CD. Of the 9 UC patients who stopped smoking after the earthquake, 7 experienced relapse (P = 0.002). Beaugerie et al. had reported that among smokers with UC who stopped smoking, disease severity increased after cessation. [23] Over the short term, smoking itself did not have an influence on relapse or remission; however, changes in smoking status caused flares in UC.

Our study had some limitations. First, we did not use validated scores that would objectively assess psychological stress such as the Cohen Perceived Stress Scale. [24] Since a huge earthquake happens suddenly, it is impossible to investigate stress several times before and after an earthquake. Therefore we assessed the degree of stress by investigating information about damage situations and changes in life styles after the Great East Japan Earthquake. Second, our study cannot disregard recall bias. It was difficult to administer a questionnaire immediately after the earthquake. That was why we obtained data about clinical characteristics and activities from both questionnaires and medical records. Third, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics may contribute to the relapse of IBD. [25] However, we think the numbers of newly prescribed NSAIDs and antibiotics during the study period were less than or equal to those of the corresponding period in the previous year. Because of the difficulty in obtaining medicines after the earthquake, the number of newly prescribed NSAIDs and antibiotics might have decreased. In addition, unlike in UC patients, twice as many males as females were among CD patients, which is in agreement with previous reports in Japan. [26 27 28] There were more current smokers among CD patients than among those with UC, in agreement with previous reports. [8 20]

Life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD. We hope that this report will help in the usual management of patients with IBD, not only

at times of catastrophic events such as a huge earthquake. For the future, a prospective study should be undertaken to determine whether stress is actually related to flares of IBD.

Contributorship statement

Hisashi Shiga and Teruko Miyazawa had the original idea for this study and were involved in writing the original study protocol, data collection and writing manuscript.

Gen Tominaga, Hiroki Takahashi, Sho Takagi, Nobuya Obana, Tatsuya Kikuchi, Shinya Oomori, Eiki Nomura, Manabu Shiraki, Yuichirou Sato, Shuichiro Takahashi, Ken Umemura, Hiroshi Yokoyama, Katsuya Endo, Yoichi Kakuta, Hiroki Aizawa, Masaki Matsuura, Tomoya Kimura and Masatake Kuroha were involved in data collection and contributed to discussion.

Yoshitaka Kinouchi, Seiichi Takahashi and Tooru Shimosegawa contributed to discussion and reviewed manuscript.

All authors had full access to all of the data in this study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no support from any organaisations for the submitted work; (2) no financial relationships with any organaisations that might have an interest in the submitted work in the previous 3 years; (3) no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was approved by the Tohoku University Hospital Committee for Clinical Investigation. Data are presented in aggregate and no personal health information is disclosed.

Data sharing

No additional data available.

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Tables

Table 1. Patients' clinical characteristics.

		Ulcerative colitis	Crohn's disease	Total
Number of patients		546	357	903
Gender				
Male		269 (49.3%)	253 (70.9%)	522 (57.8%)
Female		277 (50.7%)	104 (29.1%)	381 (42.2%)
Age	year	45.3 ± 16.6	37.1 ± 12.5	42.0 ± 15.6
Disease duration	year	9.7 ± 9.0	11.6 ± 8.1	10.5 ± 8.7
Disease extent				
Total colitis		208 (38.1%)	-	
Left-sided colitis		183 (33.5%)	-	
Proctitis		83 (15.2%)	-	
Unknown		72 (13.2%)	-	
Disease location				
Small intestine		-	61 (17.1%)	
Colon		-	212 (59.4%)	
Small intestine and colon		-	47 (13.2%)	
Unknown		-	37 (10.3%)	
Extra-intestinal complications				
Positive		51 (9.3%)	43 (12.0%)	94 (10.4%)
None		495 (90.7%)	314 (88.0%)	809 (89.6%)
Smoking status				
Current smokers		55 (10.1%)	85 (23.8%)	140 (15.5%)
Past smokers		162 (29.7%)	74 (20.7%)	236 (26.1%)
None		327 (59.9%)	198 (55.5%)	525 (58.2%)
Unclear		2 (0.3%)	0 (0.0%)	2 (0.2%)
Pregnancy experience				
Positive		181/277	41/104	222/381
(During the Earthquake)		(5)	(3)	(8)

Table 2. Use of the medications before the Great East Japan Earthquake.

		Ulcerative colitis (N=546)	Crohn's disease (N=357)	Total (N=903)	
5-ASA or SASP		486 (89.0%)	276 (77.3%)	762 (84.4%)	
PSL		79 (9.0%)	26 (7.3%)	105 (11.6%)	
	(mg)	(1-60)	(1-40)		
AZA or 6-MP		56 (10.3%)	55 (15.4%)	111 (12.3%)	
	(mg)	(15-100)	(10-100)		
Tacrolimus		4 (0.7%)	-	4 (0.4%)	
IFX		18 (3.3%)	151 (42.3%)	169 (1807%)	
	(mg)	(200-500)	(150-500)		
ADA		-	11 (3.1%)	11 (1.2%)	
TPN		0 (0.0%)	3 (0.8%)	3 (0.3%)	
ED			70 (19.6%)	70 (7.8%)	
	(kcal/day)		(300-1,800)		
CAP		3 (0.5%)	1 (0.3%)	4 (0.4%)	

5-ASA, aminosalicilic acid; SASP, salazosurufapirizine; PSL, predonisolone; AZA, azathioprine; MP, mercaptopurine; IFX, infliximab; ADA, adalimumab; TPN, total parenteral nutrition; ED, elemental diet; CAP, cytoapheresis.

Table 3. Damage and deleterious effects of the Great East Japan Earthquake.

	Ulcerative colitis (N=546)	Crohn's disease (N=357)	Total (N=903)
Damage to houses			
Total loss (≥50%)	36 (6.6%)	38 (10.6%)	74 (8.2%)
Half-loss (≥20% but <50%)	37 (6.8%)	21 (5.9%)	58 (6.4%)
Partial loss (≥3% but <20%)	236 (43.2%)	133 (37.3%)	369 (40.9%)
None	233 (42.7%)	161 (45.1%)	394 (43.6%)
Unclear	4 (0.7%)	4 (1.1%)	8 (0.9%)
Temporarily homelessness			
1 week or more	37 (6.8%)	25 (7.0%)	62 (6.9%)
Less than 1 week or none	503 (92.1%)	331 (92.7%)	834 (92.3%)
Unclear	6 (1.1%)	1 (0.3%)	7 (0.8%)
Death of family members or friends			
Yes	106 (19.4%)	69 (19.3%)	175 (19.4%)
None	435 (79.7%)	284 (79.6%)	719 (79.6%)
Unclear	5 (0.9%)	4 (1.1%)	9 (1.0%)
Changes in daily dietary intake			
Yes	153 (28.0%)	116 (32.5%)	269 (29.8%)
No	387 (70.9%)	239 (66.9%)	626 (69.3%)
Unclear	6 (1.1%)	2 (0.6%)	8 (0.9%)
Discontinuation of medications			
1 week or more	39 (9.8%)	30 (14.1%)	69 (11.7%)
None	507 (9.8%)	327 (14.1%)	834 (11.7%)
Unclear	358 (90.2%)	256 (85.9%)	614 (88.3%)
Interruption in IFX or ADA			
Yes	1/18	19/162	20/180
Complete loss of job			
Yes	26 (4.8%)	25 (7.0%)	51 (5.7%)
None	518 (94.9%)	330 (92.4%)	848 (93.9%)
Unclear	2 (0.3%)	2 (5.6%)	4 (0.4%)
Anxiety about family finances			
Yes	167 (30.6%)	145 (40.6%)	312 (34.6%)

(Short-term anxiety)*	(147)	(132)	(279)
(Long-term anxiety)*	(83)	(74)	(157)
None	376 (68.9%)	211 (59.1%)	587 (65.0%)
Unclear	3 (0.5%)	1 (0.3%)	4 (0.4%)
Changes in smoking status			
Stopped after the Earthquake	9	5	14
Restarted after the Earthquake	10	5	15

IFX, infliximab; ADA, Adalimumab. * Short-term anxiety indicates anxiety about their family finances for the next several months. Long-term anxiety indicates anxiety about their family finances several years or more in the future.

Table 4. Possible variables for relapse after the Great East Japan Earthquake.

		Odds ratio	*P* value	95% CI	
IBD type					
Ulcerative colitis	546	2.86	< 0.0001	1.73	4.87
Crohn's disease	357	1			
Gender					
Male	522	0.78	0.26	0.50	1.20
Female	381	1			
Age*					
More than 40 years	423	0.72	0.16	0.45	1.14
40 or less	479	1			
Disease duration					
More than 10 years	350	0.94	0.80	0.58	1.50
10 or less	553	1			
Extra-intestinal complications					
Positive	94	1.40	0.32	0.71	2.59
None	809	1			
Smoking status*					
Current smokers	140	0.95	0.88	0.48	1.76
Others	761	1			
Damage to houses*					
Total or half loss	132	1.01	0.97	0.52	1.88
Others	763	1			
Temporarily homelessness*					
1 week or more	62	0.97	0.94	0.41	2.14
Others	834	1			
Death of family members or friends*					
Yes	175	1.20	0.50	0.70	2.03
None	719	1			
Complete loss of job*					
Yes	51	1.55	0.31	0.65	3.47
None	848	1			
Anxiety about family finances*					

Yes	312	1.69	0.03	1.05	2.70
None	587	1			
Changes in daily dietary intake*					
Yes	269	1.83	< 0.01	1.16	2.88
None	626	1			
Discontinuation of medications					
1 week or more	69	1.49	0.30	0.69	2.98
None	834	1			

CI, Confidence interval. * Information on several patients about age, smoking status, damage to houses, temporarily homelessness, death of family members or friends, complete loss of job, anxiety about family finances, and changes in daily dietary intake was not available.

Table 5. Possible variables for remission after the Great East Japan Earthquake.

		Odds ratio	*P* value	95% CI	
IBD type					
Ulcerative colitis	546	0.81	0.58	0.39	1.72
Crohn's disease	357	1			
Gender					
Male	522	0.84	0.62	0.41	1.72
Female	381	1			
Age*					
More than 40 years	423	0.89	0.76	0.41	1.88
40 or less	479	1			
Disease duration					
More than 10 years	350	0.63	0.25	0.27	1.37
10 or less	553	1			
Extra-intestinal complications					
Positive	94	0.80	0.71	0.19	2.33
None	809	1			
Smoking status*					
Current smokers	140	0.70	0.52	0.20	1.90
Others	761	1			
Damage to houses*					
Total or half loss	132	1.07	0.90	0.33	2.86
Others	763	1			
Temporarily homelessness*					
1 week or more	62	0.82	0.81	0.12	3.40
Others	834	1			
Death of family members or friends*					
Yes	175	0.58	0.28	0.18	1.51
None	719	1			
Complete loss of job*					
Yes	51	2.23	0.28	0.47	7.87
None	848	1			
Anxiety about family finances*					

Yes	312	1.06	0.89	0.47	2.26
None	587	1			
Changes in daily dietary intake*					
Yes	269	1.26	0.55	0.58	2.62
None	626	1			
Discontinuation of medications					
1 week or more	69	0.36	0.26	0.02	1.80
None	834	1			

CI, Confidence interval. * Information on several patients about age, smoking status, damage to houses, temporarily homelessness, death of family members or friends, complete loss of job, anxiety about family finances, and changes in daily dietary intake was not available.

Original research article: Life-event stress induced by the Great East Japan Earthquake caused relapse in ulcerative colitis but not in Crohn's disease: a retrospective cohort study

Short title: Relapse of Ulcerative colitis by the Great East Japan Earthquake

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Abstract

Objective: Stress is thought to be one of the triggers of flares in patients with inflammatory bowel disease (IBD). We examined the rate of relapse in IBD patients before and after the Great East Japan Earthquake.

Design: A retrospective cohort study.

Settings: 13 hospitals in Japan.

Participants: 546 ulcerative colitis (UC) and 357 Crohn's disease (CD) patients who received outpatient and inpatient care at 13 hospitals located in the area which suffered serious damage from the earthquake. Data on patient's clinical characteristics, disease activity and deleterious effects of the earthquake were obtained from questionnaires and hospital records.

Primary outcome: We evaluated the relapse rate (from inactive to active) across two consecutive months before and two consecutive months after the earthquake, respectively. In this study, we defined "active" as conditions with a partial Mayo score = 2 or more (UC) or a Harvey-Bradshaw index = 6 or more (CD).

Results: Among the UC patients, disease was active in 167 patients and inactive in 379 patients before the earthquake. After the earthquake, activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed (relapse rate = 15.8 %). The relapse rate was about twice that of the corresponding period in the previous year. Among the CD patients, 86 patients had active

disease and 271 had inactive disease before the earthquake. After the earthquake, activity indices changed little. A total of 25 patients experienced relapse (relapse rate = 7.0 %). The relapse rate did not differ from that of the corresponding period in the previous year. Multivariate analyses revealed that UC, changes in dietary oral intake and anxiety about the family finances were associated with the relapse.

Conclusion: Life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD.

(294 words)

Keywords

earthquake, ulcerative colitis, Crohn's disease, relapse

Article summary

Article focus

Stress is thought to be one of the triggers of flares in patients with inflammatory bowel disease (IBD); however, it is not ethical to impose stressful circumstances on IBD patients in order to examine their effects.

Disease onset or aggravation of cardiovascular disease, respiratory disease, peptic ulcer, etc. was reported to increase after the huge earthquake; however, there has been no report about flares of IBD caused by the huge earthquake.

Key messages

We examined the rate of relapse in IBD patients before and after the huge earthquake, the Great East Japan Earthquake of 11 March 2011 in Japan.

Life-event stress induced by the earthquake caused relapse in ulcerative colitis (UC) but not in Crohn's disease.

This report indicates that we should take care of stress in the management of patients with IBD, especially with UC.

Strengths and limitations of this study

This is the first report that investigated activities of a large number of IBD patients before and after the huge earthquake.

We did not use validated scores that would objectively assess psychological stress, because it is impossible to investigate stress several times before and after an unexpected earthquake.

Our study cannot disregard recall bias.

Introduction

Inflammatory bowel disease (IBD) is a chronic remitting/relapsing disease. No variable has been proven to be a trigger of flares in patients with IBD. Stress has been indicated as one possible trigger of flares. [1 2 3 4 5 6 7 8] On the other hand, some reports did not prove a relationship between psychological stress and flares of IBD. [9 10 11] A prospective or well-established case-controlled study should be undertaken to determine whether stress is actually related to flares of IBD; however, it is unethical to impose stressful circumstances on IBD patients in order to examine their effects.

On 11 March 2011, Japan was hit by one of the most powerful earthquakes in recorded history, the Great East Japan Earthquake. The disaster left more than 28,000 people dead or missing, caused great damage or hardship in daily life, and also caused profound stress for all of the people, even those who did not suffer individual losses. It was surely one of the most stressful life events and might contribute to relapse in IBD patients. In terms of earthquake-induced disease onset or aggravation, cardiovascular disease, respiratory disease, diabetes mellitus, hypertension and peptic ulcer were reported to increase after the huge earthquake. [12 13 14 15 16 17] However, there has been no report about flares of IBD caused by the huge earthquake.

In this study, we examined activities of IBD patients before and after the Great East Japan Earthquake, to evaluate the relapse rate and the remission rate induced by the earthquake. We also aimed to identify factors that were related to relapse or remission of IBD.

Materials and methods

Study subjects

Thirteen hospitals (Tohoku University Hospital, Japanese Red Cross Ishinomaki Hospital, Sendai Medical Center, Takagi Clinic, Osaki Citizen Hospital, Sendai City Hospital, Japanese Red Cross Sendai Hospital, Miyagi Cancer Center, South Miyagi Medical Center and Kesennuma City Hospital in Miyagi Prefecture; Iwate Prefectural Isawa Hospital, Iwate Prefectural Chubu Hospital, Iwate Prefectural Iwai Hospital in Iwate Prefecture) participated in this study. These hospitals are located in the area that suffered serious damage from the Great East Japan Earthquake. **We sent a total of 1,080 questionnaires** to ulcerative colitis (UC) and Crohn's disease (CD) patients who received care in these hospitals. Then we examined the hospital records for data on the patients who returned a questionnaire. Hospital data contained information such as gender, age, IBD duration, disease extent (total colitis, left-sided colitis and proctitis in UC), disease location (small intestine, colon and both in CD), extra-intestinal complications, use of medications, smoking status, and pregnancy experience. Written informed consent was obtained from all participants under the protocol approved by the Tohoku University Hospital Committee for Clinical Investigation.

To evaluate the degree of stress objectively, we also obtained data about each patient's situation regarding the earthquake, such as damage to the patient's house, duration of

temporarily homelessness, deaths of family member or friends, changes in daily dietary intake, discontinuation or delay in taking medications, loss of job, family finances and changes in smoking status. We divided housing damage into 4 groups according to the degree of damage to the house; total loss (≥50%), half-loss (≥20% but <50%), partial loss (≥3% but <20%) and no damage.

We evaluated disease activity for two consecutive months before and two consecutive months after the Great East Japan Earthquake using Mayo score for UC [18] or Harvey-Bradshaw index for CD [19] that had been noted in hospital records and questionnaires. The Mayo score is comprised of information on stool frequency, rectal bleeding, findings on endoscopy and a physician's global assessment. Scores can range from 0 to 12. However, we used a partial Mayo score (range from 0 to 9) that excluded findings on endoscopy because routine endoscopic examinations were not performed so soon after the earthquake. The Harvey-Bradshaw index is comprised of information on general condition, abdominal pain, diarrhea frequency, abdominal mass and complications. Higher scores for both the Mayo score and the Harvey-Bradshaw index indicate more severe disease activity. IBD patients having a stoma were excluded because of difficulties in the count of bowel movements.

In this study, "active" was defined as follows; a partial Mayo score = 2 or more (UC) and a Harvey-Bradshaw index = 6 or more (CD). Lower scores indicated inactive disease. We defined

"relapse" as a change from inactive to active and "remission" as a change from active to inactive across the 2-months before and 2-months after the earthquake. The patients who remained active or inactive during the study period were considered to have "stable disease". We compared the relapse and remission rates with those during the corresponding period in the previous year as controls.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD). Discrete variables are presented as median and range. All statistical analyses were performed using the JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences between two groups were evaluated using chi-square test or Fisher's exact probability test, unpaired t-test or Wilcoxon signed-rank test, as appropriate. A multiple logistic regression method that included all possible variables was used. The level of statistical significance was set at $P < 0.05$.

Results

Patients' clinical characteristics

A total of 903 completed questionnaires (from 546 UC and 357 CD) were returned to us. **The response rate to the questionnaire was 83.6% (903/1080).** We examined the hospital records for each patient. Of the UC patients, 269 (49.3%) were males and 277 (50.7%) were females. The mean age of the entire group was of 45.3 ± 16.6 years and mean disease duration was 9.7 ± 9.0 years. Extent of disease was as follows; 208 patients (38.1%), total colitis (over splenic flexure); 183 (33.5%), left-sided colitis (up to splenic flexure); and 83 (15.2%), proctitis (up to rectum). Extent was unknown in 72 patients (13.2%). Among the CD patients, there were 253 males (70.9%) and 104 females (29.1%). Mean age was 37.1 ± 12.5 years and mean disease duration was 11.6 ± 8.1 years. Location of disease was as follows; 61 patients (17.1%), small intestine; 47 (13.2%), colon; and 212 (59.4%), both small intestine and colon. Location was unknown in 37 patients (10.3%) (Table 1).

Fifty-one UC (9.3%) and 43 CD (12.0%) patients experienced extra-intestinal complications. Of the UC patients, 55 patients (10.1%) were current smokers and 162 (29.7%) were past smokers. On the other hand, 85 CD patients (23.8%) were current smokers, and 74 (20.7%) were past smokers. Of 277 females with UC, 181 (65.3%) had experienced pregnancy while only 41 of 104 CD females (39.4%) had experienced pregnancy. Five UC patients and 3 CD

patients were just pregnant when the earthquake occurred (Table 1). Medications used by the IBD patients before the earthquake are shown in Table 2.

Deleterious effects of the earthquake

Of the 903 IBD patients, the houses of 501 patients (55.5%) were damaged; partial loss was experienced by 369 patients (40.9%), half-loss by 58 (6.4%), and total loss by 74 (8.2%). As a result, 62 (6.9%) patients had to stay in refuge facilities for one week or more. A total of 175 patients (19.4%) experienced the death of a family member or a friend (Table 3).

Only 51 patients (5.7%) experienced complete loss of their jobs after the earthquake. However, 279 (30.9%) and 157 (17.4%) patients felt short-term (for the next several months) and long-term (for the next several years) anxiety about their family finances, respectively (Table 3).

Because of temporarily homelessness and difficulty in getting the usual foods consumed, changes in daily intake such as fat, vegetables, fruits, etc. were experienced by 269 patients (29.8%) after the earthquake. With regard to medications, 69 patients (11.7%) interrupted medications for a week or more because they had lost their medicines or could not consult with doctors (see Table 3).

Changes in disease activity before and after the earthquake

Of the UC patients, disease was active in 167 patients (30.6%) and inactive in 379 patients (69.4%) before the earthquake. After the earthquake, activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed and disease status became inactive in 22 patients; therefore the relapse rate (from inactive to active) was 15.8% (86/546) and the remission rate (from active to inactive) was 4.0% (22/546). The relapse rate was significantly higher than in the previous year (8.8%, data not shown). On the other hand, the remission rate was significantly lower than in the previous year (8.8%, data not shown).

Of the CD patients, 86 patients (24.1%) had active disease and 271 patients (75.9%) had inactive disease before the earthquake. After the earthquake, activity indices were little changed. A total of 25 patients relapsed and disease status became inactive in 16 patients; therefore the relapse rate (from inactive to active) was 7.0% (25/357) and the remission rate (from active to inactive) was 4.5% (16/357). Unlike in UC, the relapse rate among CD patients was slightly higher than in the previous year (5.3%, data not shown), but not significantly. On the other hand, the remission rate was twice that of the previous year (2.2%, data not shown), but did not differ significantly.

Because of disease flares, 96 patients (10.6%) needed additional medications after the earthquake as follows: prednisolone (27 patients), tacrolimus (3), azathioprine (11), infliximab

(13), adalimumab (6), total parenteral nutrition (4), or others.

Possible variables for relapse or remission

There were no differences in patients' clinical characteristics between the relapse group and non-relapse group. With regard to remission, there were also no differences in patients' clinical characteristics between the remission group and non-remission group.

Multivariate analyses revealed that UC, changes in oral intake and anxiety about the family finances were independent predictors of relapse with an adjusted odds ratio (OR) of 2.86 (95% confidence interval (CI), 1.73 to 4.87), 1.83 (1.16 to 2.88) and 1.69 (1.05 to 2.70), respectively (Table 4). On the other hand, no factor was identified as an independent predictor of remission (Table 5).

Discussion

Of the 903 IBD patients, 132 patients (14.6%) had experienced damage to their houses of half or more and 175 patients (19.4%) experienced the deaths of a family member or friends. These factors confirm that the Great East Japan Earthquake had considerable power and was certainly one of the most stressful life events that could be experienced. **The response rate to the questionnaire (83.6%) was satisfactory. However, the damage caused by the earthquake might be more serious, because non-response group might include patients who took refuge in somewhere or have died.** The present study showed that life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in CD. This is the first report that investigated activities of a large number of IBD patients before and after the huge earthquake.

As for patient's clinical characteristics, gender, age, IBD duration, extra-intestinal complications and smoking status did not influence flares of IBD, with the exception of IBD type (UC or CD). As mentioned above, there have been many reports that psychological stress may induce flares of UC. [1 2 3 4 5 6 8] On the other hand, there have been few reports about flares of CD. [4 7 8] Our present study demonstrated that psychological stress caused relapse in UC, but not in CD. Other clinical characteristics, including smoking status, did not induce flares. In terms of damage and other deleterious effects from the earthquake, damage to houses, duration of

temporarily homelessness, death of family members or friends and unemployment did not induce flares of IBD; however, anxiety about family finances was related to relapse. These results may indicate that psychological stress or the uneasiness over the future have a greater influence on UC flares than direct damage and losses.

Although discontinuation of medications had no influence on flares of IBD, changes in daily dietary intake induced flares. The relation between dietary factors and the onset or flares of IBD has been reported. [20 21 22] After the earthquake, **many patients could not obtain enough food; therefore they consumed more processed foods and less raw vegetables and fruits**. With regard to possible variables for remission, we expected that the decrease in total volume or fatty foods would induce remission, especially in CD patients. However, our results did not consistent with this hypothesis. It may be due to the facts that the period of dietary restriction was not so long, and food rationing began soon. There were just few patients that had changes in smoking status after the earthquake; therefore we could not include this factor in multivariate analyses. However, changes in smoking status may be an important factor in flares of patients with UC, but not with CD. Of the 9 UC patients who stopped smoking after the earthquake, 7 experienced relapse (P = 0.002). Beaugerie et al. had reported that among smokers with UC who stopped smoking, disease severity increased after cessation. [23] Over the short term, smoking itself did not have an influence on relapse or remission; however, changes in smoking

status caused flares in UC.

Our study had some limitations. First, we did not use validated scores that would objectively assess psychological stress such as the Cohen Perceived Stress Scale. [24] Since a huge earthquake happens suddenly, it is impossible to investigate stress several times before and after an earthquake. Therefore we assessed the degree of stress by investigating information about damage situations and changes in life styles after the Great East Japan Earthquake. Second, our study cannot disregard recall bias. It was difficult to administer a questionnaire immediately after the earthquake. That was why we obtained data about clinical characteristics and activities from both questionnaires and medical records. Third, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics may contribute to the relapse of IBD. [25] However, we think the numbers of newly prescribed NSAIDs and antibiotics during the study period were less than or equal to those of the corresponding period in the previous year. Because of the difficulty in obtaining medicines after the earthquake, the number of newly prescribed NSAIDs and antibiotics might have decreased. **In addition, unlike in UC patients, twice as many males as females were among CD patients, which is in agreement with previous reports in Japan.** [26] [27] [28] There were more current smokers among CD patients than among those with UC, in agreement with previous reports. [8] [20]

Life-event stress induced by the Great East Japan Earthquake caused relapse in UC but not in

CD. We hope that this report will help in the usual management of patients with IBD, not only at times of catastrophic events such as a huge earthquake. For the future, a prospective study should be undertaken to determine whether stress is actually related to flares of IBD.

Contributorship statement

Hisashi Shiga and Teruko Miyazawa had the original idea for this study and were involved in writing the original study protocol, data collection and writing manuscript.

Gen Tominaga, Hiroki Takahashi, Sho Takagi, Nobuya Obana, Tatsuya Kikuchi, Shinya Oomori, Eiki Nomura, Manabu Shiraki, Yuichirou Sato, Shuichiro Takahashi, Ken Umemura, Hiroshi Yokoyama, Katsuya Endo, Yoichi Kakuta, Hiroki Aizawa, Masaki Matsuura, Tomoya Kimura and Masatake Kuroha were involved in data collection and contributed to discussion.

Yoshitaka Kinouchi, Seiichi Takahashi and Tooru Shimosegawa contributed to discussion and reviewed manuscript.

All authors had full access to all of the data in this study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no support from any organaisations for the submitted work; (2) no financial relationships with any organaisations that might have an interest in the submitted work in the previous 3 years; (3) no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was approved by the Tohoku University Hospital Committee for Clinical Investigation. Data are presented in aggregate and no personal health information is disclosed.

Data sharing

No additional data available.

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Life-event stress induced by the Great East Japan Earthquake was associated with relapse in ulcerative colitis but not Crohn's disease: a retrospective cohort study

Short title: Relapse of Ulcerative colitis by the Great East Japan Earthquake

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Abstract

Objective: Stress is thought to be one of the triggers of relapses in patients with inflammatory bowel disease (IBD). We examined the rate of relapse in IBD patients before and after the Great East Japan Earthquake.

Design: A retrospective cohort study.

Settings: 13 hospitals in Japan.

Participants: 546 ulcerative colitis (UC) and 357 Crohn's disease (CD) patients who received outpatient and inpatient care at 13 hospitals located in the area that were seriously damaged by the earthquake. Data on patient's clinical characteristics, disease activity and deleterious effects of the earthquake were obtained from questionnaires and hospital records.

Primary outcome: We evaluated the relapse rate (from inactive to active) across two consecutive months before and two consecutive months after the earthquake, respectively. In this study, we defined "active" as conditions with a partial Mayo score = 2 or more (UC) or a Harvey-Bradshaw index = 6 or more (CD).

Results: Among the UC patients, disease was active in 167 patients and inactive in 379 patients before the earthquake. After the earthquake, the activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed (relapse rate = 15.8 %). The relapse rate was about twice that of the corresponding period in the previous year. Among the CD patients, 86 patients had

active disease and 271 had inactive disease before the earthquake. After the earthquake, the activity indices changed little. A total of 25 patients experienced relapse (relapse rate = 7.0 %). The relapse rate did not differ from that of the corresponding period in the previous year. Multivariate analyses revealed that UC, changes in dietary oral intake and anxiety about family finances were associated with the relapse.

Conclusion: Life-event stress induced by the Great East Japan Earthquake was associated with relapse in UC but not CD.

(296 words)

Keywords

earthquake, ulcerative colitis, Crohn's disease, relapse

Article summary

Article focus

Stress is thought to be one of the triggers of relapses in patients with inflammatory bowel disease (IBD); however, it would be unethical to impose stressful circumstances on IBD patients in order to examine their effects.

Disease onset or aggravation of cardiovascular disease, respiratory disease, peptic ulcer, etc. was reported to increase after the huge earthquake; however, there has been no report about relapses of IBD associated with the huge earthquake.

Key messages

We examined the rate of relapse in IBD patients before and after a huge earthquake, the Great East Japan Earthquake of 11 March 2011 in Japan.

Life-event stress induced by the earthquake was associated with relapse of ulcerative colitis (UC) but not Crohn's disease.

This report suggests that we should take into account stress in the management of patients with IBD, especially those with UC.

Strengths and limitations of this study

This is the first report that investigated the activities of a large number of IBD patients before and after a huge earthquake.

We did not use validated scores that would objectively assess psychological stress, because it would be impossible to investigate stress several times before and after a devastating earthquake, given the usually unpredictable nature of earthquakes.

Our study cannot exclude recall bias.

Introduction

Inflammatory bowel disease (IBD) is a chronic remitting/relapsing disease. Although no variable has been proven to be a trigger of relapses in patients with IBD, stress has been described as one possibility. [1 2 3 4 5 6 7 8] On the other hand, some reports did not prove a relationship between psychological stress and exacerbations of IBD. [9 10 11] A prospective or well-established case-controlled study should be undertaken to determine whether stress is actually related to relapses of IBD; however, it would be unethical to impose stressful circumstances on IBD patients in order to examine their effects.

On 11 March 2011, Japan was hit by one of the most powerful earthquakes in recorded history, the Great East Japan Earthquake. The disaster left more than 28,000 people dead or missing, caused great damage or hardship in daily life, and also caused profound stress for all of the people, even those who did not suffer individual losses. It was surely one of the most stressful life events and might have contributed to relapses in IBD patients. In terms of earthquake-associated disease onset or aggravation, cardiovascular disease, respiratory disease, diabetes mellitus, hypertension and peptic ulcer were reported to increase after the huge earthquake. [12 13 14 15 16 17] However, there has been no report about relapses of IBD caused by the huge earthquake.

In this study, we examined the activities of IBD patients and their relapse and remission rates

before and after the Great East Japan Earthquake. We also aimed to identify factors that were related to relapse or remission of IBD.

Materials and methods

Study subjects

Thirteen hospitals (Tohoku University Hospital, Japanese Red Cross Ishinomaki Hospital, Sendai Medical Center, Takagi Clinic, Osaki Citizen Hospital, Sendai City Hospital, Japanese Red Cross Sendai Hospital, Miyagi Cancer Center, South Miyagi Medical Center and Kesennuma City Hospital in Miyagi Prefecture; Iwate Prefectural Isawa Hospital, Iwate Prefectural Chubu Hospital, Iwate Prefectural Iwai Hospital in Iwate Prefecture) participated in this study. These hospitals are located in the area that was seriously damaged by the Great East Japan Earthquake. We sent a total of 1,080 questionnaires to ulcerative colitis (UC) and Crohn's disease (CD) patients who received care in these hospitals. Then we examined the hospital records for data on the patients who returned the questionnaires. Hospital data contained information such as gender, age, IBD duration, disease extent (total colitis, left-sided colitis and proctitis in UC), disease location (small intestine, colon and both in CD), extra-intestinal complications, use of medications, smoking status, and pregnancy experience. Written informed consent was obtained from all participants under the protocol approved by the Tohoku University Hospital Committee for Clinical Investigation.

To evaluate the degree of stress objectively, we also obtained data about each patient's situation regarding the earthquake, such as damage to the patient's house, duration of

homelessness, deaths of family member or friends, changes in daily dietary intake, discontinuation or delay in taking medications, loss of job, family finances and changes in smoking status. We divided housing damage into 4 groups according to the degree of damage to the house; total loss (≥50%), half-loss (≥20% but <50%), partial loss (≥3% but <20%) and no damage.

We evaluated the disease activity for two consecutive months before and two consecutive months after the Great East Japan Earthquake using the Mayo score for UC [18] or Harvey-Bradshaw index for CD [19], depending on which was available in the hospital records and questionnaires. The Mayo score is comprised of information on stool frequency, rectal bleeding, findings on endoscopy and a physician's global assessment. Scores can range from 0 to 12. However, we used an abridged Mayo score (range from 0 to 9) that excluded findings on endoscopy because routine endoscopic examinations were not performed so soon after the earthquake. The Harvey-Bradshaw index is comprised of information on general condition, abdominal pain, diarrhea frequency, abdominal mass and complications. Higher scores for both the Mayo score and the Harvey-Bradshaw index indicate more severe disease activity. IBD patients having a stoma were excluded because of difficulties in counting bowel movements.

In this study, "active" was defined as follows: a partial Mayo score = 2 or more (UC) and a Harvey-Bradshaw index = 6 or more (CD). Lower scores indicated inactive disease. We defined

"relapse" as a change from inactive to active and "remission" as a change from active to inactive across the 2-months before and 2-months after the earthquake. The patients who remained active or inactive during the study period were considered to have "stable disease". We compared the relapse and remission rates with those during the corresponding period in the previous year as controls.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD). Discrete variables are presented as median and range. All statistical analyses were performed using the JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences between two groups were evaluated using chi-square test or Fisher's exact probability test, unpaired t-test or Wilcoxon signed-rank test, as appropriate. A multiple logistic regression method that included all possible variables was used. The level of statistical significance was set at $P < 0.05$.

Results

Patients' clinical characteristics

A total of 903 completed questionnaires (from 546 UC and 357 CD) were returned to us. The response rate to the questionnaire was 83.6% (903/1080). We examined the hospital records for each patient. Of the UC patients, 269 (49.3%) were males and 277 (50.7%) were females. The mean age was 45.3 ± 16.6 years and the mean disease duration was 9.7 ± 9.0 years. The extent of disease was as follows: 208 patients (38.1%), total colitis (over splenic flexure); 183 (33.5%), left-sided colitis (up to splenic flexure); and 83 (15.2%), proctitis (up to rectum). The extent was unknown in 72 patients (13.2%). Among the CD patients, there were 253 males (70.9%) and 104 females (29.1%). The mean age was 37.1 ± 12.5 years and the mean disease duration was 11.6 ± 8.1 years. The location of disease was as follows: 61 patients (17.1%), small intestine; 47 (13.2%), colon; and 212 (59.4%), both small intestine and colon. The location was unknown in 37 patients (10.3%) (Table 1).

Fifty-one UC (9.3%) and 43 CD (12.0%) patients experienced extra-intestinal complications. Of the UC patients, 55 patients (10.1%) were current smokers and 162 (29.7%) were past smokers. On the other hand, 85 CD patients (23.8%) were current smokers, and 74 (20.7%) were past smokers. Of 277 females with UC, 181 (65.3%) had experienced pregnancy, while only 41 of 104 CD females (39.4%) had experienced pregnancy. Five UC patients and 3 CD

patients were pregnant when the earthquake occurred (Table 1). Medications used by the IBD patients before the earthquake are shown in Table 2.

Deleterious effects of the earthquake

Of the 903 IBD patients, the houses of 501 patients (55.5%) were damaged; partial loss was experienced by 369 patients (40.9%), half-loss by 58 (6.4%), and total loss by 74 (8.2%). As a result, 62 (6.9%) patients had to stay in refuge facilities for one week or more. A total of 175 patients (19.4%) experienced the death of a family member or a friend (Table 3).

Only 51 patients (5.7%) experienced complete loss of their jobs after the earthquake. However, 279 (30.9%) and 157 (17.4%) patients reported short-term (for the next several months) and long-term (for the next several years) anxiety about their family finances, respectively (Table 3).

Because of temporary homelessness and difficulty in obtaining various types of food, changes in daily intake such as fat, vegetables, fruits, etc. were experienced by 269 patients (29.8%) after the earthquake. With regard to medications, 69 patients (11.7%) interrupted medications for a week or more because they had lost their medicines or could not consult with doctors (see Table 3).

Changes in disease activity before and after the earthquake

Of the UC patients, disease was active in 167 patients (30.6%) and inactive in 379 patients (69.4%) before the earthquake. After the earthquake, the activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed and the disease status became inactive in 22 patients; therefore, the relapse rate (from inactive to active) was 15.8% (86/546) and the remission rate (from active to inactive) was 4.0% (22/546). The relapse rate was significantly higher than in the previous year (8.8%, data not shown). On the other hand, the remission rate was significantly lower than in the previous year (8.8%, data not shown).

Of the CD patients, 86 patients (24.1%) had active disease and 271 patients (75.9%) had inactive disease before the earthquake. After the earthquake, the activity indices were little changed. A total of 25 patients relapsed and the disease status became inactive in 16 patients; therefore, the relapse rate (from inactive to active) was 7.0% (25/357) and the remission rate (from active to inactive) was 4.5% (16/357). Unlike UC, the relapse rate among CD patients was slightly higher than in the previous year (5.3%, data not shown), but not significantly. On the other hand, the remission rate was twice that of the previous year (2.2%, data not shown), but did not differ significantly.

Because of relapses, 96 patients (10.6%) required additional medication after the earthquake as follows: prednisolone (27 patients), tacrolimus (3), azathioprine (11), infliximab (13),

adalimumab (6), total parenteral nutrition (4), or others.

Possible variables for relapse or remission

There were no differences in the patients' clinical characteristics between the relapse group and non-relapse group. With regard to remission, there were also no differences in the patients' clinical characteristics between the remission group and non-remission group.

Multivariate analyses revealed that UC, changes in oral intake and anxiety about family finances were independent predictors of relapse with an adjusted odds ratio (OR) of 2.86 (95% confidence interval (CI), 1.73 to 4.87), 1.83 (1.16 to 2.88) and 1.69 (1.05 to 2.70), respectively (Table 4). On the other hand, no factor was identified as an independent predictor of remission (Table 5).

Discussion

Of the 903 IBD patients, 132 patients (14.6%) had experienced damage to their homes of half or more and 175 patients (19.4%) experienced the death of a family member or friend. These factors would suggest that the Great East Japan Earthquake was likely one of the most stressful life events for those affected. The response rate to the questionnaire (83.6%) was satisfactory. However, the damage caused by the earthquake might have been more serious, because the non-response group might have included patients who took refuge somewhere or died. The present study showed that life-event stress induced by the Great East Japan Earthquake was associated with relapse of UC but not CD. This is the first report that investigated the activities of a large number of IBD patients before and after a huge earthquake.

As for the patient's clinical characteristics, gender, age, IBD duration, extra-intestinal complications and smoking status did not influence the incidence of relapses, with the exception of IBD type (UC or CD). As mentioned above, there have been many reports that psychological stress may induce flares of UC. [1 2 3 4 5 6 8] On the other hand, there have been few reports about relapses of CD. [4 7 8] Our present study demonstrated that psychological stress was associated with relapse in UC but not CD. In terms of damage and other deleterious effects from the earthquake, damage to houses, duration of temporary homelessness, death of family members or friends and unemployment were not associated with relapses of IBD; however, anxiety about

family finances was related to relapse. These results may suggest that psychological stress or uneasiness about the future has a greater effect on UC relapses than direct damage and losses.

Although the discontinuation of medication had no influence on relapses of IBD, changes in daily dietary intake did. A relationship between dietary factors and the onset or relapses of IBD has been reported. [20 21 22] After the earthquake, many patients could not obtain enough fresh food; therefore, they consumed more processed foods and fewer fresh vegetables and fruits. With regard to possible variables related to remission, we expected that a decrease in the total volume or in fatty foods would be associated with remission, especially in CD patients. However, our results did not support this hypothesis. This may have been because the period of dietary restriction was not so long. There were few patients that changed their smoking status after the earthquake; therefore, we could not include this factor in multivariate analyses. However, changes in smoking status may have been an important factor in relapses of UC, but not CD. Of the 9 UC patients who stopped smoking after the earthquake, 7 experienced relapses (P = 0.002). Beaugerie et al. reported that among smokers with UC who stopped smoking, the disease severity increased after cessation. [23] Over the short term, smoking itself did not appear to influence relapse or remission; however, changes in smoking status were associated with relapse in UC.

Our study had some limitations. First, we did not use validated scores that could objectively

assess psychological stress such as the Cohen Perceived Stress Scale. [24] Since huge earthquakes usually happen without warning, it is impossible to investigate stress several times before and after an earthquake. Therefore, we assessed the degree of stress by examining information about damage and changes in life style after the Great East Japan Earthquake. Second, our study cannot exclude recall bias. It was difficult to administer a questionnaire immediately after the earthquake, which is why we obtained data about clinical characteristics and activities from both questionnaires and medical records. Third, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics may contribute to relapses of IBD. [25] However, we think the numbers of newly prescribed NSAIDs and antibiotics during the study period were less than or equal to those of the corresponding period in the previous year. Because of the difficulty in obtaining medicine after an earthquake, the numbers of newly prescribed NSAIDs and antibiotics might have decreased. In addition, unlike in the case of UC patients, twice as many males as females were CD patients, which is in agreement with previous reports in Japan. [26 27 28] More CD patients were current smokers than those with UC, in agreement with previous reports. [8 20]

Life-event stress induced by the Great East Japan Earthquake was related to relapses in UC but not CD. We hope that this report will be useful to the management of patients with IBD, not only during catastrophic events but also generally. For the future, a prospective study should be undertaken to determine whether stress is actually related to relapses of IBD.

Contributorship statement

Hisashi Shiga and Teruko Miyazawa had the original idea for this study and were involved in writing the original study protocol, data collection and writing manuscript.

Gen Tominaga, Hiroki Takahashi, Sho Takagi, Nobuya Obana, Tatsuya Kikuchi, Shinya Oomori, Eiki Nomura, Manabu Shiraki, Yuichirou Sato, Shuichiro Takahashi, Ken Umemura, Hiroshi Yokoyama, Katsuya Endo, Yoichi Kakuta, Hiroki Aizawa, Masaki Matsuura, Tomoya Kimura and Masatake Kuroha were involved in data collection and contributed to discussions.

Yoshitaka Kinouchi, Seiichi Takahashi and Tooru Shimosegawa contributed to discussions and reviewed the manuscript.

All authors had full access to all of the data in this study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

All authors have completed the Unified Competing Interest form at

www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) there was no support from any organisations for the submitted work; (2) no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; (3) no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was approved by the Tohoku University Hospital Committee for Clinical Investigation. Data are presented in aggregate and no personal health information is disclosed.

Data sharing

No additional data available.

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Table 1. Patients' clinical characteristics.

		Ulcerative colitis	Crohn's disease	Total
Number of patients		546	357	903
Gender				
Male		269 (49.3%)	253 (70.9%)	522 (57.8%)
Female		277 (50.7%)	104 (29.1%)	381 (42.2%)
Age	year	45.3 ± 16.6	37.1 ± 12.5	42.0 ± 15.6
Disease duration	year	9.7 ± 9.0	11.6 ± 8.1	10.5 ± 8.7
Disease extent				
Total colitis		208 (38.1%)	-	
Left-sided colitis		183 (33.5%)	-	
Proctitis		83 (15.2%)	-	
Unknown		72 (13.2%)	-	
Disease location				
Small intestine		-	61 (17.1%)	
Colon		-	212 (59.4%)	
Small intestine and colon		-	47 (13.2%)	
Unknown		-	37 (10.3%)	
Extra-intestinal complications				
Positive		51 (9.3%)	43 (12.0%)	94 (10.4%)
None		495 (90.7%)	314 (88.0%)	809 (89.6%)
Smoking status				
Current smokers		55 (10.1%)	85 (23.8%)	140 (15.5%)
Past smokers		162 (29.7%)	74 (20.7%)	236 (26.1%)
None		327 (59.9%)	198 (55.5%)	525 (58.2%)
Unclear		2 (0.3%)	0 (0.0%)	2 (0.2%)
Pregnancy experience				
Positive		181/277	41/104	222/381
(During the earthquake)		(5)	(3)	(8)

Table 2. Use of the medications before the Great East Japan Earthquake.

		Ulcerative colitis (N=546)	Crohn's disease (N=357)	Total (N=903)	
5-ASA or SASP		486 (89.0%)	276 (77.3%)	762 (84.4%)	
PSL		79 (9.0%)	26 (7.3%)	105 (11.6%)	
	(mg)	(1-60)	(1-40)		
AZA or 6-MP		56 (10.3%)	55 (15.4%)	111 (12.3%)	
	(mg)	(15-100)	(10-100)		
Tacrolimus		4 (0.7%)	-	4 (0.4%)	
IFX		18 (3.3%)	151 (42.3%)	169 (1807%)	
	(mg)	(200-500)	(150-500)		
ADA		-	11 (3.1%)	11 (1.2%)	
TPN		0 (0.0%)	3 (0.8%)	3 (0.3%)	
ED			70 (19.6%)	70 (7.8%)	
	(kcal/day)		(300-1,800)		
CAP		3 (0.5%)	1 (0.3%)	4 (0.4%)	

5-ASA, aminosalicilic acid; SASP, salazosurufapirizine; PSL, predonisolone; AZA, azathioprine; MP, mercaptopurine; IFX, infliximab; ADA, adalimumab; TPN, total parenteral nutrition; ED, elemental diet; CAP, cytoapheresis.

Table 3. Damage and deleterious effects of the Great East Japan Earthquake.

	Ulcerative colitis (N=546)	Crohn's disease (N=357)	Total (N=903)
Damage to houses			
Total loss (≥50%)	36 (6.6%)	38 (10.6%)	74 (8.2%)
Half-loss (≥20% but <50%)	37 (6.8%)	21 (5.9%)	58 (6.4%)
Partial loss (≥3% but <20%)	236 (43.2%)	133 (37.3%)	369 (40.9%)
None	233 (42.7%)	161 (45.1%)	394 (43.6%)
Unclear	4 (0.7%)	4 (1.1%)	8 (0.9%)
Temporary homelessness			
1 week or more	37 (6.8%)	25 (7.0%)	62 (6.9%)
Less than 1 week or none	503 (92.1%)	331 (92.7%)	834 (92.3%)
Unclear	6 (1.1%)	1 (0.3%)	7 (0.8%)
Death of family members or friends			
Yes	106 (19.4%)	69 (19.3%)	175 (19.4%)
None	435 (79.7%)	284 (79.6%)	719 (79.6%)
Unclear	5 (0.9%)	4 (1.1%)	9 (1.0%)
Changes in daily dietary intake			
Yes	153 (28.0%)	116 (32.5%)	269 (29.8%)
No	387 (70.9%)	239 (66.9%)	626 (69.3%)
Unclear	6 (1.1%)	2 (0.6%)	8 (0.9%)
Discontinuation of medications			
1 week or more	39 (9.8%)	30 (14.1%)	69 (11.7%)
None	507 (9.8%)	327 (14.1%)	834 (11.7%)
Unclear	358 (90.2%)	256 (85.9%)	614 (88.3%)
Interruption in IFX or ADA			
Yes	1/18	19/162	20/180
Complete loss of job			
Yes	26 (4.8%)	25 (7.0%)	51 (5.7%)
None	518 (94.9%)	330 (92.4%)	848 (93.9%)
Unclear	2 (0.3%)	2 (5.6%)	4 (0.4%)
Anxiety about family finances			
Yes	167 (30.6%)	145 (40.6%)	312 (34.6%)

(Short-term anxiety)*	(147)	(132)	(279)
(Long-term anxiety)*	(83)	(74)	(157)
None	376 (68.9%)	211 (59.1%)	587 (65.0%)
Unclear	3 (0.5%)	1 (0.3%)	4 (0.4%)
Changes in smoking status			
Stopped after the earthquake	9	5	14
Restarted after the earthquake	10	5	15

IFX, infliximab; ADA, Adalimumab. * Short-term anxiety indicates anxiety about their family finances for the next several months. Long-term anxiety indicates anxiety about their family finances several years or more in the future.

Table 4. Possible variables for relapse after the Great East Japan Earthquake.

		Odds ratio	*P* value	95% CI	
IBD type					
Ulcerative colitis	546	2.86	< 0.0001	1.73	4.87
Crohn's disease	357	1			
Gender					
Male	522	0.78	0.26	0.50	1.20
Female	381	1			
Age*					
More than 40 years	423	0.72	0.16	0.45	1.14
40 or less	479	1			
Disease duration					
More than 10 years	350	0.94	0.80	0.58	1.50
10 or less	553	1			
Extra-intestinal complications					
Positive	94	1.40	0.32	0.71	2.59
None	809	1			
Smoking status*					
Current smokers	140	0.95	0.88	0.48	1.76
Others	761	1			
Damage to houses*					
Total or half loss	132	1.01	0.97	0.52	1.88
Others	763	1			
Temporary homelessness*					
1 week or more	62	0.97	0.94	0.41	2.14
Others	834	1			
Death of family members or friends*					
Yes	175	1.20	0.50	0.70	2.03
None	719	1			
Complete loss of job*					
Yes	51	1.55	0.31	0.65	3.47
None	848	1			
Anxiety about family finances*					

Yes	312	1.69	0.03	1.05	2.70
None	587	1			
Changes in daily dietary intake*					
Yes	269	1.83	< 0.01	1.16	2.88
None	626	1			
Discontinuation of medications					
1 week or more	69	1.49	0.30	0.69	2.98
None	834	1			

CI, Confidence interval. * Information on several patients about age, smoking status, damage to houses, temporarily homelessness, death of family members or friends, complete loss of job, anxiety about family finances, and changes in daily dietary intake was not available.

Table 5. Possible variables for remission after the Great East Japan Earthquake.

		Odds ratio	*P* value	95% CI	
IBD type					
Ulcerative colitis	546	0.81	0.58	0.39	1.72
Crohn's disease	357	1			
Gender					
Male	522	0.84	0.62	0.41	1.72
Female	381	1			
Age*					
More than 40 years	423	0.89	0.76	0.41	1.88
40 or less	479	1			
Disease duration					
More than 10 years	350	0.63	0.25	0.27	1.37
10 or less	553	1			
Extra-intestinal complications					
Positive	94	0.80	0.71	0.19	2.33
None	809	1			
Smoking status*					
Current smokers	140	0.70	0.52	0.20	1.90
Others	761	1			
Damage to houses*					
Total or half loss	132	1.07	0.90	0.33	2.86
Others	763	1			
Temporary homelessness*					
1 week or more	62	0.82	0.81	0.12	3.40
Others	834	1			
Death of family members or friends*					
Yes	175	0.58	0.28	0.18	1.51
None	719	1			
Complete loss of job*					
Yes	51	2.23	0.28	0.47	7.87
None	848	1			
Anxiety about family finances*					

Yes	312	1.06	0.89	0.47	2.26
None	587	1			
Changes in daily dietary intake*					
Yes	269	1.26	0.55	0.58	2.62
None	626	1			
Discontinuation of medications					
1 week or more	69	0.36	0.26	0.02	1.80
None	834	1			

CI, Confidence interval. * Information on several patients about age, smoking status, damage to houses, temporarily homelessness, death of family members or friends, complete loss of job, anxiety about family finances, and changes in daily dietary intake was not available.

Original research article: Life-event stress induced by the Great East Japan Earthquake was associated with relapse in ulcerative colitis but not Crohn's disease: a retrospective cohort study

Short title: Relapse of Ulcerative colitis by the Great East Japan Earthquake

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Abstract

Objective: Stress is thought to be one of the triggers of relapses in patients with inflammatory bowel disease (IBD). We examined the rate of relapse in IBD patients before and after the Great East Japan Earthquake.

Design: A retrospective cohort study.

Settings: 13 hospitals in Japan.

Participants: 546 ulcerative colitis (UC) and 357 Crohn's disease (CD) patients who received outpatient and inpatient care at 13 hospitals located in the area that were seriously damaged by the earthquake. Data on patient's clinical characteristics, disease activity and deleterious effects of the earthquake were obtained from questionnaires and hospital records.

Primary outcome: We evaluated the relapse rate (from inactive to active) across two consecutive months before and two consecutive months after the earthquake, respectively. In this study, we defined "active" as conditions with a partial Mayo score = 2 or more (UC) or a Harvey-Bradshaw index = 6 or more (CD).

Results: Among the UC patients, disease was active in 167 patients and inactive in 379 patients before the earthquake. After the earthquake, the activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed (relapse rate = 15.8 %). The relapse rate was about twice that of the corresponding period in the previous year. Among the CD patients, 86 patients had

active disease and 271 had inactive disease before the earthquake. After the earthquake, the activity indices changed little. A total of 25 patients experienced relapse (relapse rate = 7.0 %). The relapse rate did not differ from that of the corresponding period in the previous year. Multivariate analyses revealed that UC, changes in dietary oral intake and anxiety about family finances were associated with the relapse.

Conclusion: Life-event stress induced by the Great East Japan Earthquake was associated with relapse in UC but not CD.

(296 words)

Keywords

earthquake, ulcerative colitis, Crohn's disease, relapse

Article summary

Article focus

Stress is thought to be one of the triggers of relapses in patients with inflammatory bowel disease (IBD); however, it would be unethical to impose stressful circumstances on IBD patients in order to examine their effects.

Disease onset or aggravation of cardiovascular disease, respiratory disease, peptic ulcer, etc. was reported to increase after the huge earthquake; however, there has been no report about relapses of IBD associated with the huge earthquake.

Key messages

We examined the rate of relapse in IBD patients before and after a huge earthquake, the Great East Japan Earthquake of 11 March 2011 in Japan.

Life-event stress induced by the earthquake was associated with relapse of ulcerative colitis (UC) but not Crohn's disease.

This report suggests that we should take into account stress in the management of patients with IBD, especially those with UC.

Strengths and limitations of this study

This is the first report that investigated the activities of a large number of IBD patients before and after a huge earthquake.

We did not use validated scores that would objectively assess psychological stress, because it would be impossible to investigate stress several times before and after a devastating earthquake, given the usually unpredictable nature of earthquakes.

Our study cannot exclude recall bias.

Introduction

Inflammatory bowel disease (IBD) is a chronic remitting/relapsing disease. Although no variable has been proven to be a trigger of relapses in patients with IBD, stress has been described as one possibility. [1 2 3 4 5 6 7 8] On the other hand, some reports did not prove a relationship between psychological stress and exacerbations of IBD. [9 10 11] A prospective or well-established case-controlled study should be undertaken to determine whether stress is actually related to relapses of IBD; however, it would be unethical to impose stressful circumstances on IBD patients in order to examine their effects.

On 11 March 2011, Japan was hit by one of the most powerful earthquakes in recorded history, the Great East Japan Earthquake. The disaster left more than 28,000 people dead or missing, caused great damage or hardship in daily life, and also caused profound stress for all of the people, even those who did not suffer individual losses. It was surely one of the most stressful life events and might have contributed to relapses in IBD patients. In terms of earthquake-associated disease onset or aggravation, cardiovascular disease, respiratory disease, diabetes mellitus, hypertension and peptic ulcer were reported to increase after the huge earthquake. [12 13 14 15 16 17] However, there has been no report about relapses of IBD caused by the huge earthquake.

In this study, we examined the activities of IBD patients and their relapse and remission rates

before and after the Great East Japan Earthquake. We also aimed to identify factors that were related to relapse or remission of IBD.

Materials and methods

Study subjects

Thirteen hospitals (Tohoku University Hospital, Japanese Red Cross Ishinomaki Hospital, Sendai Medical Center, Takagi Clinic, Osaki Citizen Hospital, Sendai City Hospital, Japanese Red Cross Sendai Hospital, Miyagi Cancer Center, South Miyagi Medical Center and Kesennuma City Hospital in Miyagi Prefecture; Iwate Prefectural Isawa Hospital, Iwate Prefectural Chubu Hospital, Iwate Prefectural Iwai Hospital in Iwate Prefecture) participated in this study. These hospitals are located in the area that was seriously damaged by the Great East Japan Earthquake. We sent a total of 1,080 questionnaires to ulcerative colitis (UC) and Crohn's disease (CD) patients who received care in these hospitals. Then we examined the hospital records for data on the patients who returned the questionnaires. Hospital data contained information such as gender, age, IBD duration, disease extent (total colitis, left-sided colitis and proctitis in UC), disease location (small intestine, colon and both in CD), extra-intestinal complications, use of medications, smoking status, and pregnancy experience. Written informed consent was obtained from all participants under the protocol approved by the Tohoku University Hospital Committee for Clinical Investigation.

To evaluate the degree of stress objectively, we also obtained data about each patient's situation regarding the earthquake, such as damage to the patient's house, duration of

homelessness, deaths of family member or friends, changes in daily dietary intake, discontinuation or delay in taking medications, loss of job, family finances and changes in smoking status. We divided housing damage into 4 groups according to the degree of damage to the house; total loss (≥50%), half-loss (≥20% but <50%), partial loss (≥3% but <20%) and no damage.

We evaluated the disease activity for two consecutive months before and two consecutive months after the Great East Japan Earthquake using the Mayo score for UC [18] or Harvey-Bradshaw index for CD [19], depending on which was available in the hospital records and questionnaires. The Mayo score is comprised of information on stool frequency, rectal bleeding, findings on endoscopy and a physician's global assessment. Scores can range from 0 to 12. However, we used an abridged Mayo score (range from 0 to 9) that excluded findings on endoscopy because routine endoscopic examinations were not performed so soon after the earthquake. The Harvey-Bradshaw index is comprised of information on general condition, abdominal pain, diarrhea frequency, abdominal mass and complications. Higher scores for both the Mayo score and the Harvey-Bradshaw index indicate more severe disease activity. IBD patients having a stoma were excluded because of difficulties in counting bowel movements.

In this study, "active" was defined as follows: a partial Mayo score = 2 or more (UC) and a Harvey-Bradshaw index = 6 or more (CD). Lower scores indicated inactive disease. We defined

"relapse" as a change from inactive to active and "remission" as a change from active to inactive across the 2-months before and 2-months after the earthquake. The patients who remained active or inactive during the study period were considered to have "stable disease". We compared the relapse and remission rates with those during the corresponding period in the previous year as controls.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD). Discrete variables are presented as median and range. All statistical analyses were performed using the JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences between two groups were evaluated using chi-square test or Fisher's exact probability test, unpaired t-test or Wilcoxon signed-rank test, as appropriate. A multiple logistic regression method that included all possible variables was used. The level of statistical significance was set at $P < 0.05$.

Results

Patients' clinical characteristics

A total of 903 completed questionnaires (from 546 UC and 357 CD) were returned to us. The response rate to the questionnaire was 83.6% (903/1080). We examined the hospital records for each patient. Of the UC patients, 269 (49.3%) were males and 277 (50.7%) were females. The mean age was 45.3 ± 16.6 years and the mean disease duration was 9.7 ± 9.0 years. The extent of disease was as follows: 208 patients (38.1%), total colitis (over splenic flexure); 183 (33.5%), left-sided colitis (up to splenic flexure); and 83 (15.2%), proctitis (up to rectum). The extent was unknown in 72 patients (13.2%). Among the CD patients, there were 253 males (70.9%) and 104 females (29.1%). The mean age was 37.1 ± 12.5 years and the mean disease duration was 11.6 ± 8.1 years. The location of disease was as follows: 61 patients (17.1%), small intestine; 47 (13.2%), colon; and 212 (59.4%), both small intestine and colon. The location was unknown in 37 patients (10.3%) (Table 1).

Fifty-one UC (9.3%) and 43 CD (12.0%) patients experienced extra-intestinal complications. Of the UC patients, 55 patients (10.1%) were current smokers and 162 (29.7%) were past smokers. On the other hand, 85 CD patients (23.8%) were current smokers, and 74 (20.7%) were past smokers. Of 277 females with UC, 181 (65.3%) had experienced pregnancy, while only 41 of 104 CD females (39.4%) had experienced pregnancy. Five UC patients and 3 CD

patients were pregnant when the earthquake occurred (Table 1). Medications used by the IBD patients before the earthquake are shown in Table 2.

Deleterious effects of the earthquake

Of the 903 IBD patients, the houses of 501 patients (55.5%) were damaged; partial loss was experienced by 369 patients (40.9%), half-loss by 58 (6.4%), and total loss by 74 (8.2%). As a result, 62 (6.9%) patients had to stay in refuge facilities for one week or more. A total of 175 patients (19.4%) experienced the death of a family member or a friend (Table 3).

Only 51 patients (5.7%) experienced complete loss of their jobs after the earthquake. However, 279 (30.9%) and 157 (17.4%) patients reported short-term (for the next several months) and long-term (for the next several years) anxiety about their family finances, respectively (Table 3).

Because of temporary homelessness and difficulty in obtaining various types of food, changes in daily intake such as fat, vegetables, fruits, etc. were experienced by 269 patients (29.8%) after the earthquake. With regard to medications, 69 patients (11.7%) interrupted medications for a week or more because they had lost their medicines or could not consult with doctors (see Table 3).

Changes in disease activity before and after the earthquake

Of the UC patients, disease was active in 167 patients (30.6%) and inactive in 379 patients (69.4%) before the earthquake. After the earthquake, the activity scores significantly increased ($P < 0.0001$). A total of 86 patients relapsed and the disease status became inactive in 22 patients; therefore, the relapse rate (from inactive to active) was 15.8% (86/546) and the remission rate (from active to inactive) was 4.0% (22/546). The relapse rate was significantly higher than in the previous year (8.8%, data not shown). On the other hand, the remission rate was significantly lower than in the previous year (8.8%, data not shown).

Of the CD patients, 86 patients (24.1%) had active disease and 271 patients (75.9%) had inactive disease before the earthquake. After the earthquake, the activity indices were little changed. A total of 25 patients relapsed and the disease status became inactive in 16 patients; therefore, the relapse rate (from inactive to active) was 7.0% (25/357) and the remission rate (from active to inactive) was 4.5% (16/357). Unlike UC, the relapse rate among CD patients was slightly higher than in the previous year (5.3%, data not shown), but not significantly. On the other hand, the remission rate was twice that of the previous year (2.2%, data not shown), but did not differ significantly.

Because of relapses, 96 patients (10.6%) required additional medication after the earthquake as follows: prednisolone (27 patients), tacrolimus (3), azathioprine (11), infliximab (13),

adalimumab (6), total parenteral nutrition (4), or others.

Possible variables for relapse or remission

There were no differences in the patients' clinical characteristics between the relapse group and non-relapse group. With regard to remission, there were also no differences in the patients' clinical characteristics between the remission group and non-remission group.

Multivariate analyses revealed that UC, changes in oral intake and anxiety about family finances were independent predictors of relapse with an adjusted odds ratio (OR) of 2.86 (95% confidence interval (CI), 1.73 to 4.87), 1.83 (1.16 to 2.88) and 1.69 (1.05 to 2.70), respectively (Table 4). On the other hand, no factor was identified as an independent predictor of remission (Table 5).

Discussion

Of the 903 IBD patients, 132 patients (14.6%) had experienced damage to their homes of half or more and 175 patients (19.4%) experienced the death of a family member or friend. These factors would suggest that the Great East Japan Earthquake was likely one of the most stressful life events for those affected. The response rate to the questionnaire (83.6%) was satisfactory. However, the damage caused by the earthquake might have been more serious, because the non-response group might have included patients who took refuge somewhere or died. The present study showed that life-event stress induced by the Great East Japan Earthquake was associated with relapse of UC but not CD. This is the first report that investigated the activities of a large number of IBD patients before and after a huge earthquake.

As for the patient's clinical characteristics, gender, age, IBD duration, extra-intestinal complications and smoking status did not influence the incidence of relapses, with the exception of IBD type (UC or CD). As mentioned above, there have been many reports that psychological stress may induce flares of UC. [1 2 3 4 5 6 8] On the other hand, there have been few reports about relapses of CD. [4 7 8] Our present study demonstrated that psychological stress was associated with relapse in UC but not CD. In terms of damage and other deleterious effects from the earthquake, damage to houses, duration of temporary homelessness, death of family members or friends and unemployment were not associated with relapses of IBD; however, anxiety about

family finances was related to relapse. These results may suggest that psychological stress or uneasiness about the future has a greater effect on UC relapses than direct damage and losses.

Although the discontinuation of medication had no influence on relapses of IBD, changes in daily dietary intake did. A relationship between dietary factors and the onset or relapses of IBD has been reported. [20 21 22] After the earthquake, many patients could not obtain enough fresh food; therefore, they consumed more processed foods and fewer fresh vegetables and fruits. With regard to possible variables related to remission, we expected that a decrease in the total volume or in fatty foods would be associated with remission, especially in CD patients. However, our results did not support this hypothesis. This may have been because the period of dietary restriction was not so long. There were few patients that changed their smoking status after the earthquake; therefore, we could not include this factor in multivariate analyses. However, changes in smoking status may have been an important factor in relapses of UC, but not CD. Of the 9 UC patients who stopped smoking after the earthquake, 7 experienced relapses (P = 0.002). Beaugerie et al. reported that among smokers with UC who stopped smoking, the disease severity increased after cessation. [23] Over the short term, smoking itself did not appear to influence relapse or remission; however, changes in smoking status were associated with relapse in UC.

Our study had some limitations. First, we did not use validated scores that could objectively

assess psychological stress such as the Cohen Perceived Stress Scale. [24] Since huge earthquakes usually happen without warning, it is impossible to investigate stress several times before and after an earthquake. Therefore, we assessed the degree of stress by examining information about damage and changes in life style after the Great East Japan Earthquake. Second, our study cannot exclude recall bias. It was difficult to administer a questionnaire immediately after the earthquake, which is why we obtained data about clinical characteristics and activities from both questionnaires and medical records. Third, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics may contribute to relapses of IBD. [25] However, we think the numbers of newly prescribed NSAIDs and antibiotics during the study period were less than or equal to those of the corresponding period in the previous year. Because of the difficulty in obtaining medicine after an earthquake, the numbers of newly prescribed NSAIDs and antibiotics might have decreased. In addition, unlike in the case of UC patients, twice as many males as females were CD patients, which is in agreement with previous reports in Japan. [26 27 28] More CD patients were current smokers than those with UC, in agreement with previous reports. [8 20]

Life-event stress induced by the Great East Japan Earthquake was related to relapses in UC but not CD. We hope that this report will be useful to the management of patients with IBD, not only during catastrophic events but also generally. For the future, a prospective study should be undertaken to determine whether stress is actually related to relapses of IBD.

Contributorship statement

Hisashi Shiga and Teruko Miyazawa had the original idea for this study and were involved in writing the original study protocol, data collection and writing manuscript.

Gen Tominaga, Hiroki Takahashi, Sho Takagi, Nobuya Obana, Tatsuya Kikuchi, Shinya Oomori, Eiki Nomura, Manabu Shiraki, Yuichirou Sato, Shuichiro Takahashi, Ken Umemura, Hiroshi Yokoyama, Katsuya Endo, Yoichi Kakuta, Hiroki Aizawa, Masaki Matsuura, Tomoya Kimura and Masatake Kuroha were involved in data collection and contributed to discussions.

Yoshitaka Kinouchi, Seiichi Takahashi and Tooru Shimosegawa contributed to discussions and reviewed the manuscript.

All authors had full access to all of the data in this study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

All authors have completed the Unified Competing Interest form at

www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) there was no support from any organisations for the submitted work; (2) no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; (3) no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was approved by the Tohoku University Hospital Committee for Clinical Investigation. Data are presented in aggregate and no personal health information is disclosed.

Data sharing

No additional data available.

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