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Stress maladjustment in the pathoetiology of ulcerative colitis

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Background. The aims of this study were (1) to measure levels of cytokines and stress hormones in ulcerative colitis (UC) patients and determine whether there were any disturbances in the nervous, endocrine, or immune systems, and (2) to measure the ability of UC patients to cope with stress (using a sense of coherence, SOC, test) and their perceived self-efficacy, and to elucidate their response to a stress load. ***Methods.*** We administered questionnaires to and took blood samples from 42 outpatients and eight inpatients whose UC was in remission, and 21 healthy volunteers. In addition, we evaluated blood samples from the inpatients and healthy volunteers following a mental calculation stress test. ***Results.*** The questionnaire results revealed that self-efficacy was significantly decreased in the patient groups. Levels of adrenocorticotropic hormone, β-endorphin and interleukin (IL)-6 were significantly higher in the outpatient than in the control group. IL-6 levels significantly increased following the mental calculation stress test in UC patients compared with in the volunteers. ***Conclusions.*** These results indicate that UC patients (1) have hypersensitive nervous, endocrine, and immune systems, and (2) this hypersensitivity was augmented by the mental calculation stress test.

Key words: cytokines, hypothalamic–pituitary–adrenal axis, mental calculation stress test, self-efficacy, stress hormone

Introduction

Ulcerative colitis (UC) is considered a stress-related disorder, and stress and disease activity are correlated.[1] Patients with UC express concerns, such as that they will impose on others when they get sick, or that they will lose their attractiveness.[2,3] In this way, UC sufferers are chronically stress-prone, and stress is liable to increase the activity of their disease. A possible explanation for the relationship between stress and UC is impairment of homeostatic maintenance mediated by the nervous, endocrine, and immune systems, including the hypothalamic–pituitary–adrenal axis (HPA-axis). It has become evident in recent years that the immune system is closely involved with stress-relieving mechanisms, in particular in relation to the nervous and endocrine systems.[4]

In a study in rats, Kojima et al.[5] showed that persistent inflammatory stress from chronic colitis causes increased production of glucocorticoids, the final product of the HPA-axis, and that these applied persistent negative feedback to the hypothalamus and pituitary glands. In a rat colitis model, Kresse et al.[6] found that the HPA-axis is chronically activated, suggesting that overexpression of stress hormones upsets its functional balance. These findings suggest that we can anticipate that chronic stress causes persistent activation of the HPA-axis, making it difficult to mount a normal stress response. In UC patients, physical, emotional, and social stresses cause disturbances in the nervous, endocrine, and immune systems, impairing their ability to respond adequately to new stressors, as well as increasing the level of stress experienced. A study of human patients with chronic inflammatory bowel disease found decreased serum levels of the adrenal hormone metabolite dehydroepiandrosterone sulfate and increased levels of cortisol,[7] however, and the relationship between disturbances in the nervous, endocrine, and immune systems, the stress response, and disease states has not been fully elucidated.

The aims of this study were (1) to measure levels of cytokines and stress hormones in UC patients, and determine whether there were any disturbances in the

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nervous, endocrine, or immune systems, and (2) to measure the ability of UC patients to cope with stress (sense of coherence, SOC) and their perceived self-efficacy, and to elucidate their response to a stress load.

Methods

Subjects

The subjects were 50 UC patients (age range, 16–64 years) in remission and under follow-up at the Saga Medical School Hospital Gastrointestinal Outpatients Department between February and October 2005. Consent to participate in this study was obtained from all 50 patients. They comprised 42 outpatients with UC in the quiescent phase (patient group A), and eight inpatients (patient group B), admitted owing to exacerbation of their disease. The eight inpatients were administered the calculation test while in a remission phase. The control group comprised 21 healthy adult volunteers matched with the patients with quiescent UC for sex and age. The criteria for quiescent phase UC in the outpatient group were a C-reactive protein (CRP) level no greater than 1.0 mg/dl, and a low assessment score (0 or 1), evaluated according to the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) system.[8] Among the eight inpatients, one had an IOIBD score of 5 points, four had a score of 4 points, one had a score of 3 points, and two had a score of 2 points. This study was conducted with the approval of the Saga Medical School Ethics Committee, and ethical guidelines were followed at all times in the conduct of this study.

Survey methods

Between 8:00 and 11:00 a.m., outpatients who had been lying down for 10 min were asked to respond to the questionnaires, and blood was taken. The inpatients, who had similarly been lying down for 10 min, also responded to the questionnaires, and blood was taken, following which they underwent a mental calculation stress test, and then additional blood samples were taken. The 21 healthy volunteers responded to the same questionnaires as the inpatient group, and then had blood taken before and after a mental calculation stress test.

Questionnaires

Survey forms

We used the General Self-Efficacy Scale (GSES),[9] developed for Japanese subjects by Sakano and Tohjoh[10] based on the General Self-Efficacy Subscale by Sherer et al.[9] The term "self-efficacy" refers to the confidence of the individual to take action to achieve a desired result. The GSES that we used comprises 16 questions, which are answered "yes" or "no," with a possible range of scores between 0 and 16. High scores denote a high degree of self-efficacy.

To measure the ability of UC patients to cope with stress, we used the Sense of Coherence (SOC) scale,[11] the validity of which has been widely demonstrated. The term "sense of coherence" refers to the ability to cope with stress, and the higher the SOC score, the better an individual is able to deal with a variety of stressors without experiencing stress. In this study, we used the shorter[12] Japanese[13] version, with 13 questions. Each question asks for a response in 1 of 7 steps, and is scored between 1 and 7, so the aggregate score will be between 13 and 91.

We used the Japanese Perceived Stress Scale (JPSS)[14] to measure the level of stress experienced by our subjects. The JPSS is the Japanese language version of the Perceived Stress Scale (PSS) developed by Cohen et al.,[15] and poses questions about the previous 1-month period, with responses scored on a 5-point scale (0–4). The range of possible scores is from 0 to 56, with higher scores indicating a high level of perceived stress.

Physiological markers

We measured immunological markers [interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF) α], endocrinological markers [corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol), and a neurological marker (β-endorphin). In consideration of diurnal variations in hormone levels, blood samples were taken between 8:00 and 11:00 a.m. Blood samples were centrifuged at 1700 g for 10 min, and then the serum was separated and preserved at –80°C. Measurements of IL-1β, IL-6, and TNF-α were performed with an enzyme-linked immunosorbent assay (ELISA) kit (Biosource International, Camarillo, CA, USA). Cortisol measurements were also performed using an ELISA kit (R&D Systems, Minneapolis, MN, USA). Measurements of CRH, ACTH, and β-endorphin were performed using an enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA, USA) Measurements of all samples were performed in duplicate.

Psychological stress test using mental calculations

We used a modified version of the calculation tests reported by Okano et al.[16] and Deanfield et al.[17] For the first 5 min of this 10-min mental calculation stress test subjects memorized six-digit numbers, then repeated these numbers in reverse (e.g., memorize 658397 and respond 793856), and then for 5 min subjects performed

Table 1. Subject demographics of the analysis groups

	Patient group A (outpatients) ($n = 42$)	Patient group B (inpatients) ($n = 8$)	Controls ($n = 21$)
Male	17	4	10
Female	25	4	11
Corticosteroid therapy	16	4	—
LCAP therapy	—	4	
IOIBD points[a]			
0	37	0	—
1	5	0	—
2–3	0	3	—
4–5	0	5	—
Mean age ± SD	36.9 ± 13.5	42.0 ± 12.5	34.8 ± 10.6
(range)	(16–64)	(25–63)	(22–60)
Disease duration,	7.6 ± 5.3	6.0 ± 6.1	—
mean ± SD (range)	(2–21)	(1–19)	—

LCAP, leukocytapheresis; IOIBD, International Organization for the Study of Inflammatory Bowel Disease
[a] IOIBD ≥ 2 means active disease

mental arithmetic (e.g., serial subtraction of 17 from 1000: 1000, 983, 966, 949, etc.).

Analyses

For comparisons of measurements between patient and control groups, and between before and after the calculation stress test, we used one of Wilcoxon's signed-rank tests, the Mann-Whitney *U* test. All statistical analyses were performed using proprietary statistical analysis software (SPSS 14.0J for Windows).

Results

Subject demographics

Subject demographics for the analysis groups are shown in Table 1. The subjects comprised 42 outpatients (17 men and 25 women), of whom 38% were on corticosteroid therapy; eight inpatients (four men and four women), of whom four were on corticosteroid therapy, with the remaining four receiving leukocytapheresis (LCAP) therapy; and 21 healthy volunteers (10 men and 11 women). Average age did not differ significantly among the three groups, and duration of illness did not differ significantly between the two patient groups.

Questionnaire results

The mean GSES score in patient group A (outpatients) was 6.70 ± 3.71, significantly lower than that of 10.24 ± 4.68 in the control group. No difference was seen in the mean SOC or JPPS scores between these groups (Table 2). These scores were not influenced by corticosteroid therapy, as there was no significant difference between UC patients receiving (16 patients) or not receiving (26 patients) corticosteroid therapy (data not shown). The α reliability coefficient was 0.832 for the GSES, 0.759 for the SOC, and 0.779 for the JPSS.

Table 2. Questionnaire results

	Patient group A ($n = 42$)	Controls ($n = 21$)
GSES	6.70 ± 3.71	10.24 ± 4.68
	*	
SOC	55.70 ± 8.79	56.00 ± 10.67
	NS	
JPSS	26.16 ± 4.53	24.90 ± 7.25
	NS	

GSES, general self-efficacy scale; SOC, sense of coherence; JPSS, Japanese Perceived Stress Scale; NS, not significant
* $P < 0.01$, Mann-Whitney *U* test

Neurological, endocrinological, and immunological markers

Serum levels of neurological, endocrinological, and immunological markers measured in the resting state are shown in Table 3.

Neurological and endocrinological markers

The mean ACTH level was significantly higher in patient group A than in the control group (1.97 ± 0.82 vs. 1.40 ± 0.56 ng/ml, $P < 0.01$), as was the mean β-endorphin level (0.81 ± 0.20 vs. 0.47 ± 0.15 ng/ml, $P <$

Table 3. Serum levels of neurological, endocrinological, and immunological markers

	Patient group A ($n = 42$)	Controls ($n = 21$)	
Cortisol (μg/dl)	8.71 ± 6.88	6.90 ± 3.16	NS
ACTH (ng/ml)	1.97 ± 0.82	1.40 ± 0.56	*
CRH (ng/ml)	3.77 ± 1.18	3.32 ± 1.31	NS
β-endorphin (ng/ml)	0.80 ± 0.20	0.47 ± 0.15	*
TNF-α (pg/ml)	3.62 ± 1.22	4.47 ± 1.47	*
IL-1β (pg/ml)	2.48 ± 0.36	2.55 ± 0.33	NS
IL-6 (pg/ml)	6.56 ± 10.06	2.05 ± 1.05	**

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, inteleukin-6
* $P < 0.01$, Mann-Whitney U test
** $P < 0.05$, Mann-Whitney U test

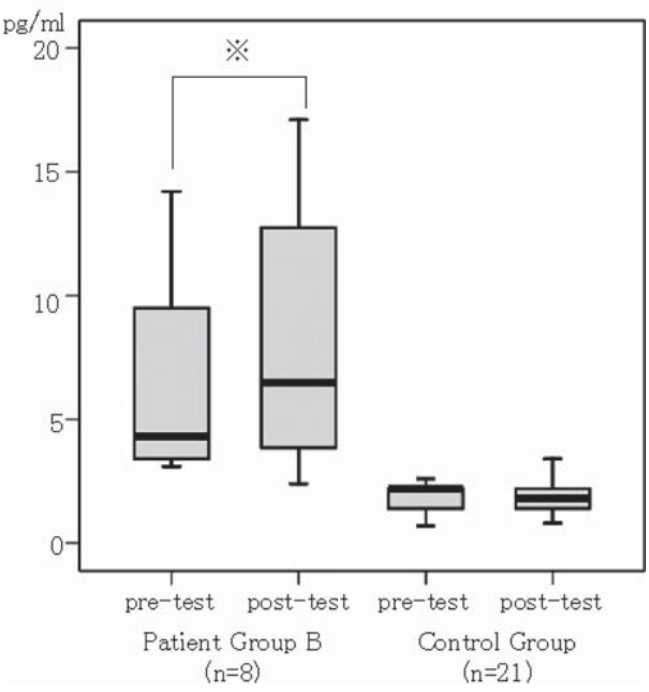

Fig. 1. Changes in interleukin (IL)-6 levels before and after the mental calculation stress test. IL-6 levels were significantly increased following the mental calculation stress test in patient group B (*$P < 0.05$). No change was seen in the control group. Statistical analysis was performed by Wilcoxon's signed-rank test

0.01). No significant differences were seen between these groups in cortisol or CRH levels.

Immunological markers

Mean TNF-α was significantly lower in patient group A than in the control group (3.62 ± 1.22 vs. 4.47 ± 1.47 pg/ml, $P < 0.05$), whereas the mean IL-6 level was significantly higher in patient group A than in the control group (6.56 ± 10.06 vs. 2.05 ± 1.05 pg/ml, $P < 0.05$). No significant differences were seen between these groups in IL-1β levels.

Relationship between questionnaire results and neurological, endocrinological, and immunological markers

We then subdivided the subject groups into low-scoring and high-scoring groups on the basis of their GSES, JPSS and SOC scores, and compared levels of physiological markers between subgroups. Similar results were seen for cortisol, β-endorphin and IL-6 between the low- and high-scoring subgroups, as shown in Table 4. No significant differences were seen in any physiological markers between the low- and high-scoring subgroups in patient group A.

Significant differences between low- and high-scoring subgroups on GSES, SOC and JPSS were seen for some markers in the control group. Significantly higher β-endorphin levels were seen in the GSES low-scoring subgroup, whereas significantly higher cortisol levels were seen in the SOC low-scoring subgroup, and in the JPSS high-scoring subgroup.

Changes in neurological, endocrinological, and immunological markers before and after the mental calculation stress test

No significant differences were seen in any markers before and after the mental calculation stress test in the control group. In patient group B, IL-6 levels increased significantly following the stress test, from 6.46 ± 4.44 pg/ml to 8.21 ± 5.70 pg/ml ($P < 0.05$) (Fig. 1).

Discussion

Raised levels of cortisol have been reported in UC patients,[7] and persistently elevated corticosterone levels have also been demonstrated in an animal model (hapten-induced chronic colitis model in rats).[5] Patients receiving corticosteroid therapy are also reported to have significantly lower cortisone levels than those not

Table 4. Relationship between questionnaire results and neurological, endocrinological, and immunological markers

	GSES				SOC			JPSS			
	n	Cortisol	β-endorphin	IL-6	*n*	Cortisol	β-endorphin	IL-6	*n*	Cortisol	β-endorphin	IL-6
Patient group A												
Low score	27	7.78 ± 6.97	0.81 ± 0.20	6.16 ± 10.41	24	7.31 ± 5.34	0.82 ± 0.20	4.70 ± 7.66	24	9.52 ± 7.80	0.80 ± 0.22	9.00 ± 12.64
High score	9	9.00 ± 6.63	0.73 ± 0.24	8.77 ± 11.25	18	10.53 ± 8.29	0.78 ± 0.21	9.01 ± 12.34	18	7.77 ± 5.59	0.83 ± 0.18	3.38 ± 3.24
Controls												
Low score	7	8.46 ± 2.71	0.56 ± 0.19*	1.93 ± 0.59	10	8.77 ± 2.35*	0.48 ± 0.09	2.14 ± 1.09	12	5.75 ± 3.20*	0.43 ± 0.11	2.18 ± 1.29
High score	12	5.97 ± 3.19	0.40 ± 0.85	1.93 ± 1.04	11	5.21 ± 2.89	0.46 ± 0.19	1.96 ± 1.05	9	8.46 ± 2.47	0.52 ± 0.18	1.87 ± 0.62

*$P < 0.05$, low vs. high scores, Mann-Whitney *U* test

on corticosteroids.[7] Usually, when cortisol levels rise, they are suppressed by negative feedback via ACTH and CRH. Our results showed that ACTH levels were significantly higher in patients with quiescent UC (patient group A) than in the control group, suggesting that the HPA-axis may not function normally in UC patients. IL-6 usually activated production of CRH, which might stimulate HPA-axis. CRH did not increase in this study, which also suggested malfunction of the HPA-axis in UC patients. We found that β-endorphin levels were significantly higher in patient group A than in the control group, possibly reflecting activation of the HPA-axis. Elevated levels of serum IL-6 have been previously reported in patients with inflammatory bowel disease.[18] High fecal levels of TNF-α are found in such patients as well, although circulating levels are low.[19] Our results showed low serum levels of TNF-α, and significantly elevated levels of IL-6, in patients with quiescent UC (patient group A).

When the level of self-efficacy is low, anxiety concerning failure increases, and mood is lowered.[20] Our results showed significantly lower GSES scores in patient group A than in the control group, suggesting that even in the quiescent phase, UC patients easily become depressed and do not adapt well to stress. Dividing each group into low-scoring and high-scoring subgroups on the basis of their GSES, SOC, and JPSSS results, we looked for differences in levels of physiological markers (cortisol, β-endorphin, IL-6). In the high JPSS score subgroup of the control group, we detected increased cortisol levels, consistent with raised cortisol secretion in response to high stress levels. This response was not seen in patient group A, suggesting inadequate production of cortisol in response to daily stress. In the low GSES score subgroup of the control group, β-endorphin levels were significantly increased, similarly suggesting overactivation of the HPA-axis in response to stress in subjects with low GSES scores. A significant difference was also seen in cortisol levels between high and low SOC score subgroups of the control group, consistent with the GSES results. None of these differences seen in the control group were seen in patient group A, indicating that the HPA-axis does not function normally in patients with UC.

Studies of stress in rheumatoid arthritis (RA) have examined changes in stress-related substances in RA patients before and after they undergo anesthesia for surgical procedures. Significant preoperative increases are seen in IL-6, cortisol, and adrenaline levels, which then drop postanesthesia.[21] These results indicate that stress-related changes in the nervous, endocrine, and immune systems play a major role in the RA disease state. In this study, IL-6 levels rose significantly in inpatients (patient group B) following the mental calculation stress test, whereas no change was seen in the

control group. This increase in IL-6, an inflammatory cytokine related to disease activity, suggests that stressors of similar magnitude to this mental calculation stress test may increase disease activity in UC patients.

There are some possible problems in interpreting the results of this study: (1) for UC patients on corticosteroid therapy, we need to interpret the results taking into account the actions of corticosteroids; (2) we used a mental calculation stress test as the stressor in this study, and future studies should use different stressors; and (3) our subject numbers were insufficient. We hope to overcome these problems in future studies.

Our results suggest that disturbances may occur in the nervous, endocrine, and immune systems of ulcerative colitis patients, and that stress may exacerbate their condition.

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