表4　偽性腸閉塞症の臨床的特徴

	患者（$n=121$）（　）内は%
症状	
腹部膨満感	90（81.0）
嘔吐	46（41.4）
腹痛	38（34.2）
便秘	30（27.0）
下痢	29（26.1）
罹患部位	
食道	14（12.3）
胃	13（11.5）
十二指腸	25（22.1）
小腸	75（66.3）
大腸	61（53.9）
直腸	1（0.8）
続発性の病因	
全身性強皮症	19（16.6）
ミトコンドリア脳筋症	6（5.2）
アミロイドーシス	4（3.5）
甲状腺機能低下症	3（2.6）
von Recklinghausen病	2（1.7）
筋強直性ジストロフィー	2（1.7）

（文献3）より一部改変）

ア機能異常による腸管運動低下の要素が最も大きいものと推測される．

また，CIP発症例は非発症例と比較して，ミトコンドリア機能異常と関連が疑われる耐糖能異常，けいれん，難聴，四肢脱力などを若年に発現する傾向があるが，CIPを初発症状とするものを認めなかった．この結果からは，ミトコンドリア機能異常を認める者の一部は病勢の進行とともに消化管機能異常を生じ，最終的にはCIPに至るという病態が推測される．

CIPは経口摂取や時には経管栄養でさえも困難な場合もあり，致命的な日常生活動作（activities of daily living；ADL）の低下をきたす可能性が高い．CIPの早期診断および早期治療，栄養状態の維持はミトコンドリア病患者の診療においても重要な要素を占めており，ミトコンドリア病患者の診療において常に念頭におくべき疾患であると言える．

慢性偽性腸閉塞診療におけるミトコンドリア病の拾い上げ

冒頭で述べた通り，CIPは一般的に慢性・再発性を示し，次第にADLの不可逆的な低下をきたす難治性疾患であるが，続発性CIPの一部に関しては原疾患，原因薬物への介入により大きく予後を改善しうると考えられる．したがって，厚生省難治性疾患克服研究事業の一環として筆者らが提案した診断基準に基づいてCIPの診断に至った全症例に関して，続発性CIPの鑑別が必要である．筆者らの研究班による，国内におけるCIP症例の文献報告の調査では，全身性強皮症（16.6%），ミトコンドリア病（5.2%），アミロイドーシス（3.5%），甲状腺機能低下症（2.6%），Von-Recklinghausen病（1.7%），筋強直性ジストロフィー（1.7%）があげられており[10]（**表4**），頻度からもミトコンドリア病の鑑別は重要であると言える．

具体的には，6か月以上前からの腹痛，膨満，嘔吐，排便障害などを慢性的に繰り返す例に対しては腹部X線，CT，消化管造影などの画像検査を行い，消化管拡張が確認され，さらに機械的消化管閉塞の除外された症例はCIPと診断することができる．CIPの診断基準を満たしたものは，さらに消化管運動異常をきたす全身性疾患を鑑別することが必須である．ミトコンドリア病の合併の検索は，CIPの家族歴があるものだけでなく，CIP症例全例に対して行うべきである．該当患者に対して，第一に耐糖能異常，けいれん，難聴，筋力低下の他，心伝導障害，脳症などの，ミトコンドリア機能障害との関連が疑われる症状および空腹時血中あるいは髄液中乳酸値・ピルビン酸値上昇の検索や好気性運動負荷試験が有用である．ミトコンドリア病が疑われる場合，筋生検での赤色ぼろ繊維（ragged-red fiber）の有無のチェックやミトコンドリア遺伝子異常の検索による確定診断の後，心電図，心臓超音波検査，脳MRI，脳波検査に

よる合併症の評価が必要となる（図2）．

おわりに

CIP診療は疾患概念の普及と同様に課題が多い分野の一つである．現時点でのCIPの治療の主体は緩下剤や運動運動促進薬，栄養療法を中心とした対症療法であるが，続発性CIPの一部は特に積極的な介入により予後の改善が見込まれる可能性がある．CIP診療においては基礎疾患としてのミトコンドリア病の存在を念頭においた診察，検査が必要である．

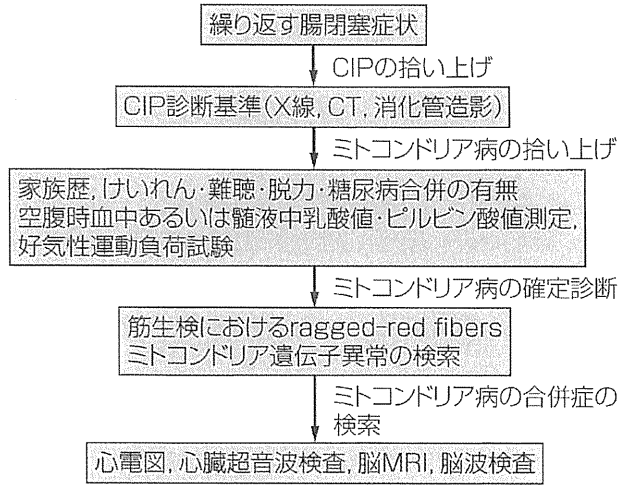

図2　CIP患者におけるミトコンドリア病診療の実際

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Imbalance in the Stress-Adaptation System in Patients With Inflammatory Bowel Disease

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Imbalance in the Stress-Adaptation System in Patients With Inflammatory Bowel Disease

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Abstract

Aim: Though inflammatory bowel disease (IBD) is known as a stress-related disorder, basic evidence for this claim is lacking. The current study was performed to investigate the function of the neuroendocrine-immune system as a main pathway in stress response and stress-coping ability and the associations among stress response, stress-coping ability, and disease activity in IBD patients. **Method:** A questionnaire was administered to obtain information concerning stress state and stress-coping ability (self-efficacy and sense of coherence [SOC]) in 78 IBD patients and 21 healthy volunteers. Blood samples were taken for determining the serum levels of various stress-related hormones and cytokines before and after a calculation stress test. **Results:** Self-efficacy was significantly decreased in patients, though the degree of perceived stress and SOC did not differ between patients and controls. Basal levels of cortisol did not differ, but levels of adrenocorticotropic hormone, β-endorphin and interleukin (IL)-6 were significantly higher in patients than in controls. In addition, the control group, but not the patient group, demonstrated significant differences in the basal cortisol levels between low and high SOC subgroups and between low and high perceived stress subgroups. Furthermore, IL-6 levels were significantly increased following the calculation stress test in patients only. **Conclusion:** Results indicate that IBD patients may have skewed neuroendocrine-immune systems and that emotional stress may aggravate the disease. Stress-management interventions might be useful, not only for patients' quality of life (QOL) but also for disease control.

Keywords

stress-adaptation system, neuroendocrine-immune system, hypothalamic-pituitary-adrenal (HPA) axis, hormone, cytokine, pathomechanism, inflammatory bowel disease

Many reports have indicated a possible correlation between a patient's perception of stress and disease activity in inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (Brown, 1963; Drossman et al., 1991; Moser et al., 1995), but most of these reports were uncontrolled observational studies with little scientific significance (North, Clouse, Spitznagel, & Alpers, 1990). A recent review assessing the epidemiological evidence regarding a causal link between stress and gut inflammation in IBD showed some consistent evidence for a contribution of psychological factors to IBD disease course; however, results of psychological interventions in IBD were mostly negative (Maunder & Levenstein, 2008). Another recent article, in which prospective clinical studies on the effect of psychological stress on IBD were carefully reviewed, showed that 13 of 18 such studies demonstrated significant relationships between stress and adverse outcomes; however, methodology varied among studies (Cámara, Ziegler, Begré, Schoepfer, & von Känel, 2009). Thus, the possible association between stress and disease activity in IBD remains controversial, and more rigorous studies are needed.

The pathomechanical basis for an association between stress and disease activity in IBD patients is unclear at present. One possibility is impairment of the stress-adaptation system, now widely accepted to be the neuroendocrine-immune system, including the hypothalamic-pituitary-adrenal axis (HPA axis). When the limbic system is stimulated upon initiation of the stress response, the hypothalamus is activated, leading to the secretion of corticotropin-releasing hormone (CRH) and

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stimulation of the sympathetic nervous system. Upon CRH stimulation, the pituitary gland secretes adrenocorticotropic hormone (ACTH) and β-endorphin, leading to the secretion of glucocorticoid by the adrenal cortex. Glucocorticoid has anti-inflammatory, immunosuppressive, and antitumor action, acting primarily as a mediator in the stress-adaptation system to maintain the homeostasis of the living body.

In a study using rats, Kojima and colleagues (2002) showed that persistent inflammatory stress from chronic colitis caused continuously increased production of glucocorticoids, the final product of HPA axis activation, leading to persistent negative feedback to the hypothalamus and pituitary glands. In a rat colitis model, Kresse, Million, Saperas, and Tache (2001) found that the HPA axis was chronically activated in colitis, suggesting that persistent overexpression of stress hormones upset the functional balance of the HPA axis. In chronic colitis in humans, patients would be expected to have perceptions of long-standing stress; under such chronic stressful conditions, continuously elevated glucocorticoid levels can suppress the secretion of CRH and ACTH, possibly resulting in a functional disturbance of the HPA axis. Thus, chronic stress may cause persistent activation of the HPA axis, making it difficult to show a normal stress response.

In addition to the neuroendocrine system (HPA axis), the immune system is closely involved in the homeostatic control of the stress-adaptation system (Mawdsley & Rampton, 2005). Cytokines are mediators in the inflammatory-immune system, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, interferon (IFN)-γ, IL-4, and IL-10, most of which are related to homeostatic maintenance during stress (Maes et al., 1998). Usually the activation of the stress-adaptation system results in a shift toward inhibition of cellular immune response and production of proinflammatory cytokines such as IL-1, IL-6, and TNF-α. However, under certain conditions, stress hormones and the activation of the HPA axis may actually facilitate inflammation through induction of proinflammatory cytokine production (Elenkov, 2008). Proinflammatory cytokines, in turn, stimulate glucocorticoid secretion by promoting CRH secretion in the hypothalamus and by directly stimulating the adrenal gland. Thus, the relationships among stress and the resultant inflammatory or anti-inflammatory response in the neuroendocrine-immune system are complicated and remain to be elucidated further.

As described, in IBD patients, various long-lasting physical (disease associated or inflammatory), emotional, and social stresses may cause persistent malfunction of the stress-adaptation system (neuroendocrine-immune system), which may lead to patients being unable to respond adequately to new stressors and possibly to disease exacerbation. Researchers have reported decreased serum levels of dehydroepiandrosterone sulfate (DHEAS), an adrenal hormone metabolite, and increased levels of cortisol in IBD patients (Straub, Vogl, Gross, Lang, Scholmerich, & Andus, 1998). However, the evidence for functional disturbance in the neuroendocrine-immune systems of IBD patients is scarce, and the associations between such disturbances and stress-coping ability and disease activity have not been fully studied.

Two social–psychological concepts, self-efficacy and sense of coherence (SOC), are also thought to be related to individuals' stress-coping ability but have not been investigated in detail in IBD patients. Bandura introduced the concept of *self-efficacy* in his social learning theory (Bandura's social cognitive theory) as people's beliefs about their capabilities to perform at the level necessary to exercise influence over events that affect their lives. Self-efficacy beliefs determine how people feel, think, motivate themselves, and behave (Bandura, 1994). According to this theory, when a person takes a certain action, a result prediction and an effect prediction arise. A result prediction is the prediction that one's action results in some consequences. On the other hand, an effect prediction is a prediction for how effectively one can perform the task. Self-efficacy is the degree of recognition of how strong an effect one is able to have. Previous research has shown that patients with chronic diseases having high levels of self-efficacy show less reaction to psychological stress and less development of depression and anxiety than patients with lower levels of self-efficacy, suggesting a close relation between self-efficacy and stress-coping ability (Kim, Shimada, & Sakano, 1996).

In contrast, SOC is a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that one's internal and external environments are predictable and that there is a high probability that things will work out as well as can reasonably be expected (Antonovsky, 1993). Thus, SOC expresses the degree of certainty that one can stay healthy when confronted with stressful situations.

Our hypothesis in the study described here was that IBD patients have disturbances in their stress-adaptation systems and also decreased actual stress-coping ability, probably caused by chronic physical or pathological stress in addition to emotional and social stress related to disease suffering, leading to inadequate responses to new stressors as well as further disease exacerbation. The aims of the current study were (a) to determine whether there was a disturbance in the stress-adaptation functions of the neuroendocrine-immune system in IBD patients, in association with the pathomechanism of the disease, by comparing serum levels of stress hormones and cytokines between IBD patients and healthy controls and by comparing these serum markers before and after a calculation stress test and (b) to clarify the association of these stress hormone levels with self-efficacy and SOC as they relate to stress coping.

Materials and Method

Participants

Participants in the IBD group comprised 78 IBD patients (age range 16–63 years), 21 with Crohn's disease and 57 with ulcerative colitis, who were seen at a university hospital located in southern Japan between February 2005 and October 2007 (see Table 1). Of the 150 patients followed for this period, who

Table 1. Subject Demographics for Patients with Inflammatory Bowel Disease (IBD) Patients and Healthy Controls

Characteristic	Patients ($n = 78$)	Controls ($n = 21$)
Male/female (n)	36/42	10/11
Age (years; $M \pm SD$ [range])	36.6 ± 14.5 (16–63)	34.8 ± 10.6 (22–60)
Diagnosis (n [%])		
Crohn's disease	21 (27)	NA
Ulcerative colitis	57 (73)	NA
Undergoing corticosteroid therapy (n [%])	32 (41)	NA
Disease duration (years; $M \pm SD$ [range])	6.81 ± 5.19 (2–21)	NA

were in a quiescent phase based on the criteria for quiescent phase IBD proposed by the International Organization for the Study of Inflammatory Bowel Disease (C-reactive protein level no greater than 1.0 mg/dl and a low assessment score [0 or 1]; Myren et al., 1984), 67 were excluded from the study. Some were deemed ineligible by their physicians due to their characters or symptoms (e.g., nervous or depressive) and some did not visit the hospital on any of our study days. An additional five patients did not consent to participate. There were no significant differences in age, sex, or disease characteristics between the 78 patients with inactive IBD, who enrolled in the study and the 72 who did not. Among the 78 patients enrolled in the study, we performed the calculation stress test in only 25 because this test required further time and some were unwilling to take such a stress-loading test. In addition, 21 healthy adult volunteers recruited from hospital and university staff, who were age- and sex-matched with the patients, were studied as the control group. All of the patients and control subjects gave informed consent to participate in the study. This study was conducted with the approval of the medical school's Ethics Committee, and ethical guidelines were followed throughout the study.

Survey Protocols

We took blood samples and asked participants in the IBD group to complete study questionnaires between 8:00 and 11:00 a.m. Participants had been lying down for more than 10 min prior to the blood draw. Thereafter, some of the IBD group participants underwent the mental calculation stress test, and further blood samples were taken. The 21 healthy volunteers similarly completed the questionnaires and had blood taken before and after the mental calculation stress test.

Questionnaires

We used the Japanese version of the General Self-Efficacy Scale (GSES; Sakano & Tojo, 1986), which is based on the original GSES (Sherer et al., 1982). We used a general self-efficacy scale, rather than a more specific one, because we used the same instrument to measure self-efficacy in the healthy controls for a comparison. The scale is composed of 16 yes/no questions, with a possible range of scores of 0–16. High scores denote a high degree of self-efficacy.

For the measurement of SOC, we used the SOC scale (Antonovsky, 1996), the validity of which has been widely demonstrated. SOC is considered to be closely related to the ability to cope with stressors (Urakawa & Yokoyama, 2009); the higher an individual scores on the SOC, the less stress that individual is expected to experience when dealing with a variety of stressors. In the current study, we used the shorter Japanese version of the scale, which has 13 questions (Callahan & Pincus, 1995; Togari & Yamazaki, 2005). In each question participants are asked to choose one of seven options, and scores for each range between 1 and 7. Range for total score on the scale is 13–91.

In addition, we used the Japanese Perceived Stress Scale (JPSS; Iwahashi, Tanaka, Fukudo, & Hongo, 2002) to measure the level of stress experienced by participants. The JPSS is the Japanese version of the Perceived Stress Scale and has 14 questions (Cohen, Kamarck, & Mermelstein, 1983). The scale measures comprehensively the degree of perceived stress associated with daily life and future concerns as well as stressful life events during the previous 1-month period. Participants answer each question on a 5-point scale (0–4). The range of possible scores is 0–56, with higher scores indicating higher levels of perceived stress. The a reliability coefficients in the present study were .832 for the GSES, .759 for the SOC, and .779 for the JPSS.

Physiological Markers

We studied the serum levels of immunological markers (IL-1β, IL-6, and TNF-α), endocrinological markers (CRH, ACTH, and cortisol), and a neurological marker (β-endorphin). In consideration of diurnal variation and the unstable nature of hormone levels, we took all of the blood samples between 8:00 and 11:00 a.m. after participants had been lying down for at least 10 min. Blood samples were centrifuged at 3,000 rpm for 10 min; serum was separated and preserved at −80°C until it was analyzed. Levels of IL-1β, IL-6, TNF-α, and cortisol were measured using an ELISA kit (Biosource International Inc., Camarillo, California, and R&D Systems, Minneapolis, Minnesota, USA). Measurement of CRH, ACTH, and β-endorphin was performed using an EIA kit (Phoenix Pharmaceuticals Inc., Belmont, California, USA). All of the measurements were performed in duplicate.

Table 2. Mean ± *SD* Scores for Patients with Inflammatory Bowel Disease (IBD) and Healthy Controls on Study Questionnaires

Questionnaire	Patients ($n = 78$)	Controls ($n = 21$)	p
GSES	7.05 ± 3.56	10.2 ± 4.68	<.01
SOS	53.84 ± 9.92	56.00 ± 10.67	NS
JPSS	26.51 ± 5.09	24.90 ± 7.25	NS

Note. GSES = General Self-Efficacy Scale; JPSS = Japanese Perceived Stress Scale; NS = not significant; SOC = Sense of Coherence scale. Statistical analyses performed by Mann-Whitney *U* test.

Psychological Stress Test Using Mental Calculations

In order to determine whether there was a difference between IBD patients and normal controls in the response of the neuroendocrine-immune system to a new stress, we administered a mental calculation stress test to 25 IBD patients and 21 healthy subjects. We used a modified version of a calculation test that was confirmed to have an influence equal to exercise stress on blood pressure and heart rate (Deanfield et al., 1984; Okano, Utsunomiya, & Yano, 1998). Briefly, for the first 5 min we asked participants to memorize six-digit numbers then to repeat these numbers in reverse (e.g., memorize 658397 and respond 793856). For the next 5 min, we asked participants to perform mental arithmetic (e.g., serial subtraction of 17 from 1,000: 1,000, 983, 966, 949, etc).

Statistical Analyses

For comparison of various measurements between patient and control groups and of the serum levels of the physiological markers between the groups before and after the calculation stress test, we used Mann-Whitney's *U* test because there were not normal distributions in some of the variables in both patients and controls. All statistical analyses were performed using proprietary statistical analysis software (SPSS 14.0J for Windows).

Results

Subject Demographics

Demographics for the patients and controls are shown in Table 1. Patients comprised 78 inactive IBD patients, 36 males and 42 females, of whom 32 (41%) were on low-dose corticosteroid therapy (<15mg/day). The control group was composed of 21 age- and sex-matched healthy volunteers, 10 males and 11 females.

Questionnaire Results

The mean GSES scores were 7.05 ± 3.56 for IBD patients and 10.23 ± 4.68 for controls, showing a significant difference ($p < .01$; see Table 2). No difference was seen in the mean SOC or JPSS scores between patients and controls. These scores were not influenced by corticosteroid therapy, since there were no significant differences in these scores between IBD patients with and without corticosteroid therapy (data not shown).

Neurological, Endocrinological, and Immunological Markers

Serum levels of neurological, endocrinological and immunological markers measured in the resting state are shown in Table 3. Mean ACTH level was significantly higher in the patient group than in the control group ($p < .01$) as was the mean β-endorphin level ($p < .01$). As for the proinflammatory cytokines, mean concentration of IL-1β was lower in IBD patients than in controls. However, serum levels of IL-1β and of TNF-α remained low, almost within the physiological range, in both groups. In contrast, mean IL-6 level was significantly higher in IBD patients than in controls ($p < .01$) and was beyond the physiological range.

When comparing these markers between patients taking steroids and those not taking them, we found no significant differences in serum levels except for β-endorphin levels, with those taking steroids having significantly lower levels (Table 3). However, β-endorphin level in IBD patients as a group was high as compared with healthy controls, as described above, indicating that high levels of β-endorphin in patients might not be connected with the fact that some of the patients were taking steroids. These results suggest that in the current study, the influence of corticosteroid therapy is negligible on the estimation of the serum markers studied.

Relationships Between SOC and Self-Efficacy and Physiological Markers

In looking at possible correlations between the SOC and Self-Efficacy scores and the physiological markers, we found a significant correlation ($r = -0.647$, $p < .05$) only between serum cortisol level and SOC score in the control group (data not shown). We then subdivided subjects into low SOC and high SOC score subgroups on the basis of the criteria for SOC scoring (male: $0 \leq$ low score ≤ 24, $25 \leq$ high score ≤ 56; female: $0 \leq$ low score ≤ 25, $26 \leq$ high score ≤ 56; Antonovsky, 1996) and compared levels of various physiological markers between subgroups (Table 4). We similarly subdivided subjects into low and high GSES (for males: $0 \leq$ low score ≤ 8, $9 \leq$ high score ≤ 16; for females: $0 \leq$ low score ≤ 7, $8 \leq$ high score ≤ 16) and JPSS ($0 \leq$ low score ≤ 56, $57 \leq$ high score ≤ 91; Iwahashi et al., 2002; Sakano & Tojo, 1986) score subgroups. In the control group, we found significantly higher cortisol levels in the low SOC score and high JPSS score subgroups. In addition, we found significantly higher β-endorphin levels in the low GSES-score subgroup of control subjects. In contrast, we found no significant differences in any physiological markers between the low and high score subgroups of IBD patients.

Changes in Physiological Markers Before and After Mental Calculation Stress Test

A total of 25 IBD patients and 21 healthy controls performed the mental calculation stress test. We found no significant differences in any physiological markers before and after the

Table 3. Comparison of *M* ± *SD* Levels of Neurological, Endocrinological, and Immunological Markers in Patients With Inflammatory Bowel Disease (IBD) and Healthy Controls

		Patients			*p* Value	
Marker	Controls ($n = 21$)	Total ($n = 78$)	Steroids ($n = 32$)	No Steroids ($n = 46$)	Controls vs. Patients	Steroids vs. No Steroids
Cortisol (μg/dl)	6.90 ± 3.16	8.75 ± 9.27	8.69 ± 8.02	8.99 ± 8.12	NS	NS
ACTH (ng/ml)	1.40 ± 0.56	1.97 ± 1.06	2.18 ± 1.33	1.86 ± 0.83	<.01	NS
CRH (ng/ml)	3.32 ± 1.31	3.55 ± 1.25	3.40 ± 1.02	3.69 ± 1.40	NS	NS
β-endorphin (ng/ml)	0.47 ± 0.15	0.83 ± 0.77	0.64 ± 0.26	0.98 ± 0.97	<.01	<.05
TNF-α (pg/ml)	4.47 ± 1.47	3.81 ± 1.42	3.67 ± 1.18	3.88 ± 1.59	NS	NS
IL-1β (pg/ml)	2.55 ± 0.33	2.30 ± 0.65	2.34 ± 0.48	2.31 ± 0.72	<.01	NS
IL-6 (pg/ml)	2.05 ± 1.05	8.0 ± 16.37	11.16 ± 23.69	6.83 ± 8.67	<.01	NS

Note. ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; IL = interleukin; NS = not significant; TNF-α = tumor necrosis factor-alpha. Statistical analyses performed by Mann-Whitney *U* test.

Table 4. Comparison of *M* ± *SD* Levels of Physiological Markers Between Patients With Inflammatory Bowel Disease (IBD) and Healthy Control Subjects Grouped by Score Level for the GSES, SOC, and JPSS Instruments

	Patients					Controls				
	Low		High			Low		High		
Instrument and Marker	*n*	*M* ± *SD*	*n*	*M* ± *SD*	*p* Value	*n*	*M* ± *SD*	*n*	*M* ± *SD*	*p* Value
GSES	47		31			7		14		
Cortisol		7.73 ± 6.55		7.60 ± 8.12	NS		8.56 ± 2.41		6.14 ± 3.17	NS
β-endorphin		0.68 ± 0.25		1.06 ± 1.17	NS		0.56 ± 0.17		0.42 ± 0.10	< .05
IL-6		9.08 ± 19.98		7.60 ± 8.12	NS		1.92 ± 0.57		2.11 ± 1.24	NS
SOC	45		33			10		11		
Cortisol		8.39 ± 8.47		9.28 ± 7.28	NS		8.77 ± 2.35		5.21 ± 2.89	< .05
β-endorphin		0.91 ± 0.98		0.72 ± 0.23	NS		0.48 ± 0.09		0.46 ± 0.19	NS
IL-6		4.88 ± 4.64		13.66 ± 24.17	NS		2.14 ± 1.09		1.96 ± 1.05	NS
JPSS	39		39			12		9		
Cortisol		9.02 ± 8.54		8.47 ± 7.42	NS		5.75 ± 3.20		8.46 ± 2.47	< .05
β-endorphin		0.81 ± 0.09		0.85 ± 0.86	NS		0.43 ± 0.11		0.52 ± 0.18	NS
IL-6		12.15 ± 22.00		4.67 ± 4.29	NS		2.18 ± 1.29		1.87 ± 0.62	NS

Note. Statistical analyses performed by Mann-Whitney *U* test. GSES = General Self-Efficacy Scale (males: 0 ≤ low score ≤ 8, 9 ≤ high score ≤ 16; females: 0 ≤ low score ≤ 7, 8 ≤ high score ≤ 16); JPSS = Japanese Perceived Stress Scale (0 ≤ low score ≤ 56, 57 ≤ high score ≤ 91); NS = not significant; SOC = Sense of Coherence scale (male: 0 ≤ low score ≤ 24, 25 ≤ high score ≤ 56; female: 0 ≤ low score ≤ 25, 26 ≤ high score ≤ 56); IL-6 = interleukin-6.

stress test in the control group (Table 5). However, in IBD patients, IL-6 levels increased significantly following the stress test ($p < .01$).

Discussion

IBD is known as stress-related disorder, and stress management is believed to have a significant effect on patients' quality of life (QOL) and also on the disease itself (Goodhand & Rampton, 2008; Vidal et al., 2008). However, there have been few reports indicating actual evidence of stress maladaptation in IBD patients or of significant associations between the function of the stress-adaptation system and the pathomechanism of human IBD. In the current study, we examined whether the neuroendocrine-immune system functioned normally as a stress-adaptation system in IBD patients and whether stress increased disease activity.

Researchers have reported elevated cortisol levels in IBD patients (Straub et al., 1998), and persistently elevated corticosterone levels have been demonstrated in an animal model (hapten-induced chronic colitis model in rats; Kojima et al., 2002). Usually, when cortisol levels rise, they are suppressed by negative feedback via suppression of ACTH and CRH secretion. In the current study, serum cortisol levels in the patients were high compared to those of healthy controls, though not significantly so. However, contrary to our expectation, ACTH levels were significantly higher in IBD patients than in the control group, suggesting that negative feedback in the HPA axis may not function sufficiently in IBD patients. One potential confounding factor in the measurement of cortisol levels appears not to have influenced the current results.

Table 5. Serum Levels of Physiological Markers in Patients with Inflammatory Bowel Disease (IBD) and Healthy Controls Before and After the Mental Calculation Stress Test

	Patients (n = 25)			Controls (n = 21)		
Marker	Pretest	Posttest	p Value	Pretest	Posttest	p Value
Cortisol (μg/dl)	8.07 ± 10.38	7.54 ± 10.64	NS	6.90 ± 3.16	6.45 ± 3.43	NS
ACTH (ng/ml)	1.81 ± 1.40	2.28 ± 1.86	NS	1.40 ± 0.56	1.53 ± 0.69	NS
CRH (ng/ml)	3.26 ± 1.51	3.41 ± 1.47	NS	3.32 ± 1.31	3.46 ± 1.43	NS
β-endorphin (ng/ml)	0.88 ± 1.36	0.82 ± 1.36	NS	0.47 ± 0.15	0.49 ± 0.14	NS
TNF-α (pg/ml)	3.96 ± 1.32	3.84 ± 1.28	NS	4.47 ± 1.47	4.50 ± 1.35	NS
IL-1β (pg/ml)	2.02 ± 0.89	2.17 ± 1.02	NS	2.55 ± 0.33	2.50 ± 0.31	NS
IL-6 (pg/ml)	13.17 ± 25.74	14.55 ± 26.09	<.01	2.05 ± 1.05	1.98 ± 0.92	NS

Note. ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; IL = interleukin; NS = not significant; TNF-α = tumor necrosis factor-alpha. Statistical analyses performed by Mann-Whitney *U* test.

Though patients receiving corticosteroid therapy are reported to have significantly different serum cortisol levels from those not on corticosteroids (Straub et al., 1998), in the current study cortisol levels did not differ between patients taking corticosteroids and those not taking them. All of the patients in the study were inactive, so among the patients taking steroids, the dose was relatively small (less than 15 mg/day).

β-Endorphin is a neurotransmitter that has endogenous morphine-like anodynic action. In the current study, serum β-endorphin levels were higher in patients than in controls, suggesting possible activation of the HPA axis in IBD patients, which may provide partial relief of symptoms.

Cytokines are the essential mediators in inflammatory/immune responses and are known to be involved in the stress-adaptation system. In the current study, three proinflammatory cytokines (TNF-α, IL-1β, and IL-6) that have been implicated in the pathoetiology of IBD, were studied in relation to stress adaptation. Previously, elevated levels of serum IL-6 have been reported in IBD patients (Kmiec, 1998), and TNF-α has been shown to be highly expressed in intestines of these patients (Braegger, Nicholls, Murch, Stephens, & McDonald, 1992), though other researchers have found serum levels of TNF-α to be low (Nielsen, Brynskov, & Bendtzen, 1993). In the current study, we found that serum IL-6 levels were significantly higher in IBD patients than in controls but that TNF-α and IL-1β levels were low both in patients and controls, consistent with the results reported previously. Serum IL-6 levels in IBD patients are associated with disease activity, and IL-6 activates CRH production in the hypothalamus, suggesting that highly increased IL-6 levels might continue to stimulate the HPA axis in IBD patients.

According to Bandura (1977), when the level of self-efficacy is low, anxiety concerning failure increases and mood is lowered. Our results showed significantly lower GSES scores in IBD patients than in the controls, suggesting that even in the inactive phase, IBD patients easily become depressed and may not sufficiently adapt to stress. However, contrary to our expectations, there were no significant differences between patients and controls in the SOC score, which is generally associated with the ability to cope with stress. This finding may be partly explained by the fact that SOC hardly changes over time, being a reflection of an individual's own character rather than of more situational factors. Therefore, this tool may not actually detect changes in stress-coping ability. We found no significant differences between patients and controls in JPSS scores, suggesting that the degree of perceived stress was almost the same in the two groups.

In examining the associations between questionnaire results (GSES, SOC, and JPSS) and serum levels of physiological markers (cortisol, β-endorphin, and IL-6), we had some interesting findings. First, the control subjects having a high degree of daily perceived stress (JPSS) showed increased cortisol levels, as we expected. However, the IBD patients did not show such a difference in cortisol levels between those with high and low JPSS scores, suggesting that cortisol production in IBD might not be sufficient in response to daily stress. Second, control subjects having low self-efficacy showed increased β-endorphin levels and a tendency toward high cortisol levels, as expected, suggesting that the HPA axis was further activated in the controls with low levels of self-efficacy. But, again, the IBD patients did not show such a difference between low and high scorers. Third, the control subjects having low SOC showed increased cortisol levels, as expected, suggesting that the HPA axis was further activated in the control subjects who might have lower stress-management ability, similar to the case of self-efficacy. However, once again, the IBD patients showed no difference in cortisol levels between low and high scorers at all. Taken together, these findings suggest that the HPA axis in IBD patients might not function normally.

The calculation stress test revealed another interesting difference between the IBD patients and the healthy controls. Control subjects showed no change in serum neurological, endocrinological, and immunological markers from pre- to posttest. However, in the IBD patients, the proinflammatory IL-6 level, which was already high before the calculation stress test, further increased after the test. Interestingly, cortisol levels did not show any significant change from pre- to posttest in the patients or the controls, which differed from our expectations. It may be that the stress of the calculation test was too weak to produce any change in serum cortisol level. The increased level

of IL-6 in response to the calculation stress test in the patient group only suggests that even a weak mental stress may trigger inflammatory activation in IBD patients, though no actual exacerbation was seen in patients during the study. We believe this is the first finding demonstrating an association between stress loading and the pathomechanism (possible exacerbation) of IBD.

Previously, in patients with rheumatoid arthritis (RA), another stress-related inflammatory disorder, mirthful laughter caused a significant decrease in serum IL-6 concentration in the patients who had high basal levels of IL-6 as compared to healthy controls (Yoshino, Fujimori, & Kohda, 1996). Researchers also reported on the changes in stress-related substances in RA patients before and after they underwent anesthesia (presumed to be a stress-free state) for surgical procedures (Hirano, Nagashima, Ogawa, & Yoshino, 2001). In their report, levels of IL-6, cortisol, and adrenalin, which were increased before anesthesia significantly dropped following anesthesia, indicating that stress-related changes in the neuroendocrine-immune system might play a significant role in the disease state of RA. Results of the current study suggest that IBD patients may have an imbalance in HPA axis function, probably due to chronic perceived stress and/or possibly the inflammatory disease, itself, resulting in inappropriate release of stress-related substances including proinflammatory cytokines, which may cause further exacerbation of the disease.

Study Limitations

In the current study, the size of the subject groups, 78 IBD patients versus 21 controls at baseline (before the calculation stress test), was unbalanced. This imbalance may limit a proper group comparison at baseline; thus further studies with matched and sufficiently sized patient and control groups are needed. Also, serum samples would ideally be taken at multiple time points because most of the serum markers studied are released in a pulsatile manner. However, because of the subject inconvenience and extra time and costs, we took serum sample only twice, before and after the calculation stress test. The condition and time of the blood draws were kept as similar as possible among subjects to minimize bias and variations. Finally, it is preferable to examine only patients without steroid treatment for an analysis of stress hormones because the current assay could not distinguish exogenous from intrinsic glucocorticoid metabolites. However, in order to recruit a sufficient number of patients, we included both patients taking steroids and those not. We confirmed that there were no significant differences in serum concentrations of most of the markers, including cortisol, between these two subgroups, indicating that the influence of corticosteroid therapy could be negligible.

Implications for Nursing

Our findings in the current study suggest that the neuroendocrine-immune system in IBD patients may not function normally, possibly due to high levels of long-standing perceived stress, which may cause inappropriate responses to current stressors and result in possible disease deterioration. Thus, interventions for improving the ability to cope with stress may be helpful in preventing disease exacerbation and improving QOL in IBD patients. For example, interventions such as instruction in stress management and relaxation techniques and peer counseling programs are thought to be useful. In addition, self-management programs in which patients learn to accept the facts of living with a disease may be helpful. Lorig and colleagues (1999) recently demonstrated the usefulness of a self-management program developed by Lowry, which includes components of both stress-management and relaxation programs, for improving QOL in patients with various chronic diseases. This program yielded significant increases in self-efficacy and significant improvements of health state (decreased number of clinic visit and hospitalization days; Lorig, Sobel, Ritter, Laurent, & Hobbs, 2001). Milne, Joachim, and Niedhardt (1986) reported that an intervention designed to develop autogenic techniques, personal planning skills, and communication techniques had improved Crohn's disease activity index and IBD stress index. Furthermore, Kennedy and colleagues (2004) reported that IBD patients who had completed a self-management program made fewer hospital visits without increasing the number of primary care visits, as compared to the same patients' number of visits before the intervention.

Based on our current findings and the previous findings reported above, it is important that health care providers realize that IBD patients may have an imbalance in their stress-adaptation systems. It may thus be effective to introduce an appropriate intervention, such as stress-management or self-management programs, for IBD patients.

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