大うつ病患者における微熱の自覚症状

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九州大学医学部附属病院心療内科外来を1年間に受診した914名の新患全員を対象として、大うつ病における微熱の頻度と両者の関連を検討した。診断名と主訴に加えて、調査票で微熱の有無を調査し、Logistic回帰分析を行った。大うつ病を有する群の37%、有しない群の22%が調査票で微熱があると回答した。男性ないし女性における大うつ病の診断や女性におけるSDS（Self-rating Depression Scale）の高値は調査票での微熱の存在と統計学的に有意な関連を認めた。男女の大うつ病あるいは女性のSDS高値は微熱を関連すると結論され、微熱を訴える患者の診察においては、鑑別診断に大うつ病を入れることが適切診断治療と医療費削減につながると考えられる。

Key words：大うつ病、微熱自覚症状、調査票

2005年8月1日受稿、2006年2月10日受理
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心身医・2006年10月・第46巻第10号

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Self-reported Low-grade Fever in Major Depression

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Abstract

Objectives: To investigate the prevalence of a self-reported low-grade fever in patients with depression and the association between self-reported low-grade fever and major depression.

Subjects: 914 new outpatients, who consulted the clinic of the Department of Psychosomatic Medicine at Kyushu University Hospital in the course of a year.

Method: A multivariate questionnaire was used to survey whether or not subjects experienced a low-grade fever, in addition to determining their chief complaints and the diagnosis. Logistic regression analysis was used for the statistical analyses.

Results: Self-reported low-grade fever was found in 37% of the subjects with major depression and 22% of the subjects without major depression. Major depression (OR 2.40, 95%CI 1.35-4.25, p<0.005 in males; OR 2.09, 95%CI 1.34-3.24, p<0.005 in females) and high Self-rating Depression Scale (SDS) scores in females (OR 1.82, 95%CI 1.40-2.35, p<0.0001) were associated with self-reported low-grade fever.

Conclusion: Major depression in both genders and a high SDS score in females were associated with low-grade fever. When treating patients complaining of fever, testing for depressive disorder in differential diagnoses may contribute to proper diagnosis and treatment of depressive disorder, which can reduce medical costs.

Key words: major depression, self-reported low-grade fever, questionnaire

Introduction

It is widely recognized that various somatic as well as psychiatric symptoms accompany depression. The most widespread somatic symptoms often cited in the literature are insomnia, general fatigue, weight loss, digestive organ dysfunction, circulatory organ dysfunction, and neurological symptoms3-4). Since widespread brain
dysfunction is observed in depression, it is natural to suppose that the thermoregulation mediated by the central nervous system is associated with depressive disorder. However, there have been very few reports on thermoregulatory disorders in depressive patients. In the present study, we investigated the prevalence of self-reported low-grade fever in Japanese patients with a major depression and examined the possible association between such fever and major depression in tertiary medical care.

Material and methods

1 Subjects

The study was performed on all 914 outpatients, who consulted the clinic of the Department of Psychosomatic Medicine of Kyushu University Hospital for the first time between June 2000 and March 2001. Although new patients were to be referrals, approximately half of them were walk-in patients at our tertiary medical care center. After examination by the preexamination physician in order to make a provisional diagnosis, the patients were assigned to the attending physicians and given a complete checkup.

2 Assessment of symptoms

At the preliminary examination, patients, who had given written consent, were asked to describe their three chief complaints and reply to questionnaires including Kyudai Medical Index (KMI), a modification of the Cornell Medical Index–Health Questionnaire, and Self-rating Depression Scale (SDS). KMI consists of 102 yes or no questions, including 2 comprehensive questions, 2 questions about past history, 2 questions about family history, 50 questions about psychiatric symptoms and 46 questions about somatic symptoms including a question: “Do you feel you have a low-grade fever?” This question was used to investigate the patient’s self-reported low-grade fever. In SDS, subjective psychiatric symptoms associated with depressive disorders were assessed.

The criteria for a diagnosis of major depression were as follows. When both the preexamination physician and the attending physician made a diagnosis of major depression according to the diagnostic criteria in DSM-IV, the patient was included in the group with major depression. When neither made a diagnosis of depression, the patient was included in the group without major depression. When either made a diagnosis of a major depression and the other did not, the KMI answers were checked. The KMI covers all the symptoms necessary for diagnosis of major depression in DSM-IV: depressive mood, loss of interest, weight loss/appetite loss, insomnia/hypersomnia, retardation of thought/difficulty in concentration, easy fatigability, guilt feeling, psychomotor impatience/inhibition, and suicidal ideation. Our investigation thus centered on whether or not the KMI answers met the diagnostic criteria for major depression. When the criteria were met, the patient was included in the group with depression. Otherwise, the patient was excluded from the analyses. According to the criteria, the group with and without major depression consisted of 335 and 422 subjects, respectively, out of 914, and 157 subjects were excluded from the analyses.

Among them, 708 (316 depressive and 392 non-depressive patients) remained conclusively because of missing values in the KMI questions.

3 Statistical Analysis

Univariate and multiple logistic regres-
sion analyses were performed. The outcome variable was a self-reported low-grade fever assessed by the KMI. The explanatory variable was major depression or 10-point increase in the SDS score. In the multivariate analysis, diagnoses by the attending physicians corresponding to anxiety disorder, eating disorder, or somatoform disorder according to DSM-IV were adjusted. Adjusted odds ratio (OR) and 95% confidence interval (CI) were obtained from the corresponding logistic regression coefficients and their standard errors. All analyses were performed using Stata version 7.0 (StataCorp. College Station, Texas, USA).

Results

Table 1 shows the demographic data of these 708 patients, who were the subjects of the analyses. The age of the male (p < 0.05) and female (p < 0.0001) subjects and the SDS scores (p < 0.0001) of subjects with major depression were significantly higher than those without. Diagnoses corresponding to anxiety disorder in DSM-IV accounted for 16.1% in men and 15.6% in women, eating disorders were 2.3% in men and 12.5% in women, and somatoform disorders were 3.4% in men and 3.1% in women.

In the KMI questionnaire, the most frequent symptoms were lack of refreshment (80.4%), concern about physical condition (78.1%), and incubus (76.0%). Convulsion (3.1%) and autoeroticism/nocturnal eminence (5.1%) were the least common symptoms. The incidence of self-reported low-grade fever assessed by the KMI was as high as 28.6%, while only 2.7% indicated fever as their chief complaint. In subjects with major depression, the prevalence of low-grade fever in KMI ranged up to 37.0%. All patients with fever as their chief complaint also reported fever in the KMI.

Table 2 shows the association between self-reported low-grade fever and major depression. Simple logistic regression analysis revealed a significant correlation between self-reported low-grade fever and major depression in men, women, and both genders (OR 2.09; 95% CI 1.50-2.91). In the multiple logistic regression analysis adjusted for anxiety disorder, eating disorder, and somatoform disorder, the association was also statistically significant in men, women, and both genders (OR 2.17; 95% CI 1.54-

| Table 1 Demographic characteristics of subjects |
|------------------|------------------|------------------|------------------|
|                  | Depression       | Non-depression   | Total            |
| Number (%)       |                 |                  |                  |
| Men              | 101 (39.0)      | 158 (61.0)       | 259 (100)        |
| Women            | 215 (47.9)      | 234 (52.1)       | 449 (100)        |
| Total            | 316 (44.6)      | 392 (55.4)       | 708 (100)        |
| Age              |                 |                  |                  |
| Men*             | Mean 40.0       | SD 17.1          | Mean 34.6        |
| Women**          | Mean 40.8       | SD 16.9          | Mean 33.2        |
| Total**          | Mean 40.5       | SD 17.0          | Mean 33.8        |
| SDS              |                 |                  |                  |
| Men**            | Mean 55.1       | SD 8.4           | Mean 45.5        |
| Women**          | Mean 56.0       | SD 7.7           | Mean 47.9        |
| Total**          | Mean 55.7       | SD 7.9           | Mean 46.9        |

SDS: Zung Self-rating Depression Scale
Age and SDS score of major depression group were significantly higher than in those without major depression.
*p < 0.05, **p < 0.0001
The association between self-reported low-grade fever and SDS scores is shown in Table 3. Since the OR was approximately 1 if the explanatory variable was a single score increase in SDS score, a 10-point increase in SDS scores was chosen as the explanatory variable. In women, the correlation was statistically significant according to both simple logistic regression (OR 1.84; 95% CI 1.43–2.40) and multiple logistic regression (OR 1.82; 95% CI 1.40–2.35). In contrast, neither simple logistic regression analysis (OR 1.26; 95% CI 0.94–1.67) nor multiple logistic regression analysis (OR 1.23; 95% CI 0.92–1.65) revealed a statistically significant correlation in men.

**Discussion**

In the present study, the KMI questionnaires revealed self-reported low-grade fever in as much as 37.0% (38.6% in men and 36.3% in women) among outpatients of both genders with major depression. It was significantly more prevalent than in subjects without major depression. Self-reported low-grade fever was associated with major depression and a high SDS score.

In the previous report targeting 100 patients with depression at a family prac-
tice clinic, only 10% complained of chills or fever. In the present study, only 2.7% of the subjects cited fever as a chief complaint (data not shown). However, when responding to the KMI questionnaire, as many as 28.7% reported the sensation of low-grade fever, which is much higher than in the previous report. This result indicates that there are many patients with a latent thermoregulation disorder, who are not recognized as such from their chief complaints.

On investigating atypical symptoms of psychiatric disease, there seems to be an essential difference between analyzing by verbally probing for chief complaints and the questionnaire approach. The latter seems less susceptible to somatization than chief complaints and seems to have been quite useful in detecting many more patients with the complaint.

In the present study, some somatic chief complaints including low-grade fever negatively correlated with the SDS scores, possibly because of somatization (our unpublished observation). For patients with somatization, complaining of a somatic symptom may function as a "ticket of admission", as stated by Simon et al. The psychiatric severity in patients suffering from somatization and reporting fever as their chief complaint may have been greatly underestimated, since such patients tend to mention psychiatric symptoms less as chief complaints or in the questionnaires. Thus, analyses by chief complaints are susceptible to somatization. In the present study, usage of a questionnaire to detect low-grade fever made it possible to detect the association between the symptom and major depression or between the symptom and high SDS scores.

There have been some reports on the association between body temperature and psychiatric disorders. Some refer to abnormalities in the circadian rhythm of body temperature such as a nocturnal rise in body temperature, phase delay, premature phase, or an attenuation of amplitude. Tsujimoto et al. also reported a positive correlation between the average body temperature and the Hamilton Rating Scale for Depression in a group consisting of normal subjects and subjects with various psychiatric disorders. However, they did not observe any difference in the average body temperature between the patients and the control subjects. In earlier reports surveying the somatic symptoms of depression, fever or low-grade fever was not mentioned. In the present study, it was indicated that self-reported low-grade fever was related to not only a diagnostic parameter of major depression assessed by DSM-IV, but also a psychometric parameter of depression measured by the SDS.

The mechanisms of fever in depression remain unclear. In animal experiments, cyclooxygenase inhibitors have been reported to be ineffectual for anticipatory hyperthermia, which is a kind of psychogenic stress-induced rise in body temperature. This report coincides with clinicians' experience that nonsteroidal anti-inflammatory drugs are not effective for some febrile patients. A kind of antidepressant, imipramine, has been reported to be effective for stress-induced hyperthermia in mice. There have been many reports on impairment of cortisol response and hypothermic responses to serotonin 1A agonist. Thus, serotoninergic neurotransmission might be involved in the fever of depressive patients.

In the previous report, 29.9% of patients with fever of unknown origin (FUO)
remained without any definite diagnosis after a standardized diagnostic protocol\textsuperscript{22}. It is possible that low-grade fever of some depressive patients is treated by the same strategy as for infectious diseases, remains immedicable, and is then categorized as a fever of unknown origin. If depression were one of the diagnostic decision branches, early diagnosis of such conditions as depressive disorder would be possible and contribute to an overall reduction in medical costs.

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