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①Influence of alexithymia on the prognosis of patients with major depression

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Influence of alexithymia on the prognosis of patients with major depression

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Abstract : Background: Alexithymia has been reported to hinder psychotherapeutic outcome. However, whether alexithymia influences the pharmacotherapeutic outcome of patients with major depression is unknown. The purpose of this study was to explore whether alexithymia predicts the prognosis of major depression patients treated with pharmacotherapy.

Methods: A prospective study was undertaken in 26 inpatients with major depression. Patients were treated with pharmacotherapy in a naturalistic setting. At baseline, the patients' scores on the 20-item Toronto Alexithymia Scale (TAS-20) and the Zung Self-rating Depression Scale (SDS) and other socio-demographic and medical data were obtained. Six months after discharge, outcome data (presence or absence of being at work and presence or absence of readmission after discharge) were obtained.

Results: A logistic regression analysis revealed that low TAS-20 scores and being unmarried were associated with being at work at 6 months after discharge in the participants. No factor was significantly associated with the presence of readmission in this sample.

Conclusions: Our findings suggested that alexithymia might be associated with the six-month prognosis in patients with major depression treated with pharmacotherapy. Individual traits such as alexithymia should be taken into account when we formulate the strategy to improve the prognosis of patients with major depression.

Key words : Alexithymia, Major depression, Prognosis, Pharmacotherapy

INTRODUCTION

Alexithymia is a well known psychological characteristic involving difficulty in expressing emotions and in identifying their own feelings. The concept initially evolved from clinical observations of patients with psychosomatic disorders;

the term was introduced by Nemiah and Sifneos during the early 1970s¹⁾. Alexithymia is a common condition, existing in about 10% of healthy people. It has been reported to exist at even higher rates not only in individuals with psychosomatic disease but also in those with panic disorder, posttraumatic stress disorder, eating disorders, and substance abuse disorders, among other conditions²⁾. Alexithymia is now considered a possible risk factor in various psychiatric diseases.

Historically, based on extensive clinical observations, alexithymic patients has been reported and paid attention to as a poor responder to psychoanalysis or other insight-oriented forms of psychotherapy²⁾. On the other hand, in Japan, treatment resistant modern type of depression has increased, and heterogeneity of major depression has been paid attention³⁾. But, the influence of alexithymia on the prognosis of major depression is still unclear⁴⁾.

In the STAR*D study, after an unsatisfactory response to citalopram (Level 1 treatment), patients who consented to random assignment to either cognitive therapy or alternative pharmacologic strategies (Level 2 treatment) had generally comparable outcomes. Level 2 treatment, whether cognitive therapy or alternative pharmacologic strategies, resulted in having less response rates than Level 1 treatment^{5,6)}. That is, a poor responder to pharmacotherapy might be also a poor responder to psychotherapy, and both therapies are similar in response rates in major depressive disorder patients. Moreover, in major depressive disorder patients, pharmacotherapy and psychotherapy has considerable similar changes between before and after treatments in the brain function^{7,8)}. Therefore, alexithymic major depressive disorder patients who might be treatment resistant to psychotherapy also might be treatment resistant to pharmacotherapy.

Major depression is a common disease, with 15% life prevalence⁹⁾. However, about 20% -30% of patients with major depression have been reported to be treatment-resistant^{5,10)}. Investigations of the factors related to the prognoses of major depression are important for the development of more effective treatments.

The purpose of the present study was to explore whether alexithymia predicts the prognosis of patients with major depression treated with pharmacotherapy.

METHODS

1. Study sample and procedure

Patients meeting the following criteria were drawn consecutively from the inpatient population of the Psychiatry Unit of Hiroshima University Hospital during the 23-month period from January 2003 to November 2004:

- (1) A psychiatric diagnosis of major depressive episode (major depression) was determined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) by a trained psychiatrist at the patient's admission
- (2) 20 years of age or older
- (3) absence of cognitive impairment
- (4) absence of a history of manic or hypomanic episodes
- (5) absence of the other axis I psychiatric disorders

This study was approved by the Institutional Review Board and the Ethics Committee of Hiroshima University Hospital, Japan. Written informed consent was obtained from each subject before the start of this study. Patients were treated with pharmacotherapy and supportive therapy (mainly with pharmacotherapy) in a naturalistic setting.

First, eligible patients received an explanation of this study from their physician in the Psychia-

try Division, and then, if they consented to participate, were fully informed of the purpose of the study. Written consent was obtained from eligible patients, and an interview was then arranged at a day (Time1: baseline) within one week from the day of admission to the psychiatric ward. Sociodemographic and medical data were obtained from the patient's medical record and in a structured interview by a trained psychiatrist.

At 6 months after the patient's discharge (Time2), outcome data (i.e., presence or absence of being at work, readmission to the psychiatric ward after discharge) and amounts of antidepressant taken daily (converted to imipramine equivalent) at discharge were obtained from their brief interview and from their medical record. Being at work means that not only being registered to his/her office but also really (and regularly) working then, without regard to full time or part time. Because alexithymic patients have difficulty of identifying feelings, we adopted not the index of depressive symptoms but the indices of social functioning such as being at work or readmission as outcome variables.

2. Measurement

Zung Self-rating Depression Scale (SDS)

The degree of depression was measured by the Japanese version of the Zung Self-rating Depression Scale (SDS). The SDS is a self-report questionnaire with 20 items rated on a four-point scale¹¹⁾. Fukuda and Kobayashi¹²⁾ reported that the Japanese version of the SDS has high validity and reliability. A high SDS score indicates a high degree of depression.

The 20-Item Toronto Alexithymia Scale (TAS-20)

The degree of alexithymia was measured using the Japanese version of the 20-Item Toronto Alexithymia Scale (TAS-20). The TAS-20 is a self-report questionnaire with 20 items rated on a five-point scale with a three-factor structure: (1)

difficulty in identifying feelings, (2) difficulty in describing feelings, and (3) externally oriented thinking. Previous studies indicated that the TAS-20 has adequate validity and reliability^{13,14)} and that the Japanese version of the TAS-20 has high construct validity and reliability¹⁵⁾. In the present study, the TAS-20 total score was used as an index of the degree of alexithymia, with a high TAS-20 score indicating a high degree of alexithymia.

3. Statistical analysis

The presence versus absence of being at work (employment) at Time2, and readmission versus no readmission during the 6-month period from discharge were entered into the analysis as dependent variables. Associated factors were assessed by univariate and multivariate analyses. First, we performed a univariate analysis between the presence/absence of being at work at Time2 and the presence/absence of readmission during the 6-month post-discharge period, and then we examined the patients' sociodemographic and medical factors (at Time1, except for the amounts of antidepressant) to determine possible independent variables by the chi-square test, T-test, or Mann-Whitney U-test. Dummy variables were used when independent variables were categorical.

We then determined the final risk factors by applying a stepwise logistic regression analysis with the presence/absence of being at work at Time2 or the presence/absence of readmission during the 6-month post-discharge period as the dependent variables, entering all independent variables. Differences with a p-value <0.05 were considered significant, and p-values <0.15 were considered a significant tendency. All p-values reported here are two-tailed. We used SPSS Version 10.0J statistical software (SPSS, Chicago, IL, USA) for all of the data analyses.

Table 1. Univariate analysis of the factors associated with presence of being at work at 6 months after discharge in patients with major depression (n=26)

Patient characteristics at baseline		Being at work		<i>p</i> -value
		Present (n=10)	Absent (n=16)	
Gender				
Male	18	8	10	0.347*
Female	8	2	6	
Age (years)	48.8 ± 12.2 [†]	44.4 ± 13.0 [†]	51.5 ± 11.3 [†]	0.154***
Education (years)	13.5 ± 3.0 [†]	13.8 ± 2.4 [†]	13.4 ± 3.5 [†]	0.737**
Marital status				
Married	23	8	15	0.286*
Unmarried	3	2	1	
Employment status				
Employed	13	7	6	0.107*
Unemployed	13	3	10	
Family history of psychiatric disease				
Yes	6	2	4	0.768*
No	20	8	12	
SDS	49.8 ± 9.7 [†]	46.7 ± 10.8 [†]	51.8 ± 8.8 [†]	0.315***
TAS-20	56.5 ± 7.9 [†]	53.1 ± 8.3 [†]	58.7 ± 7.1 [†]	0.050***
Antidepressant (mg) [#]	157.7 ± 115.0 [†]	170.0 ± 107.7 [†]	150.0 ± 122.2 [†]	0.676**
Hospitalization (days)	49.7 ± 25.6 [†]	41.5 ± 16.2 [†]	54.8 ± 29.3 [†]	0.203**

* chi-square test, ** t-test, *** Mann-Whitney U-test

[#] Imipramine equivalent amount (at discharge)

[†] mean ± SE

RESULTS

1. Patient characteristics

Of the 34 eligible patients, 8 (23.5%) declined to participate in the study. Thus, the data available for the 26 patients (76.5%) who responded were used in the analysis. Age, gender, and psychiatric diagnosis data for the 8 patients who were eligible but did not participate in the study were available. There were no significant differences between the participants (n=26) and non-participants (n=8) in any available data.

The participating patients' characteristics (**Table 1**) include the following: 18 males (69.2%), 8 females; the mean age was 48.8 ± 12.2 (standard deviation [SD]); the mean years of education was 13.5 ± 3.0; 23 (88.5%) were married; 13 (50.0%) were not employed; 6 (23.0%) patients had a

family history of psychiatric disease; the mean amount of daily antidepressant was 157.7 ± 115.0 mg; the mean duration of hospitalization was 49.7 ± 25.6 days.

2. Factors correlated with being at work and readmission in patients

Table 1 summarizes the results of the univariate analysis of the factors associated with being at work at Time2 among the participants with major depression. Among the investigated variables, being employed (p=0.107), and low TAS-20 score (p=0.050) showed a tendency of being associated with being at work at Time2 in the participants with major depression.

Similarly, the univariate analysis of the factors associated with readmission during the 6-month post-discharge period in the participants with major depression were performed. Among the

Table 2. Logistic regression analysis of the factors associated with presence of being at work at 6 months after discharge in patients with major depression (n=26)

	Beta	SE	Odds ratio	95% CI	<i>p</i>
Marital status	- 5.818	2.584	0.003	0.000-0.471	0.024
TAS-20	- 0.217	0.107	0.805	0.653-0.993	0.043
Employment status	2.573	1.532	13.102	0.650-263.880	0.093

R^2 (Cox & Snell) = 0.393, R^2 (Nagelkerke) = 0.533

investigated variables, a family history of psychiatric treatment ($p=0.146$) showed a tendency of being associated with readmission during the 6-month post-discharge period.

Table 2 shows the results of the logistic regression analysis of factors associated with being at work at Time2 in the participants with major depression. The factors associated with being at work at Time2 in the participants with major depression were being unmarried ($p=0.024$) and low TAS-20 score ($p=0.043$).

We also conducted a logistic analysis to identify the factors associated with readmission during the 6-month post-discharge period in the participants with major depression. We found that no factors were significantly associated with readmission during the 6-month post-discharge period in this group.

DISCUSSION

We found that in patients with major depression, low degrees of alexithymia and unmarried status might be related to being at work at 6 months after hospitalization.

1. Factors related to being at work in patients with major depression

Low degrees of alexithymia was correlated with being at work at 6 months post-hospitalization in the patients with major depression. Conversely, high degrees of alexithymia was correlated with not being at work in this population.

Although the reason for this correlation is not

clear, there are several possible explanations. The salient feature of alexithymia is difficulty identifying and describing subjective feelings¹⁾. That is, not being at work in alexithymic people may be related to a deficit in emotional regulation that reflects both deficits in the cognitive-experiential component of emotion response systems (i.e., deficits in the top-down regulation from the higher-order brain regions, such as language areas to the limbic structure) and deficits at the level of interpersonal regulation of emotion (i.e., an inability to express one's emotions and to get support from others)¹⁶⁾.

On the other hand, one of the salient features of alexithymia is constricted imaginal capacities¹⁾. Our previous findings suggested that alexithymic people have a disturbance of future happy imagery¹⁷⁾. Thus, alexithymic people might have difficulty in producing future happy imagery about their working life, and this could reduce their motivation for work.

Moreover, brain regions which have been reported to be associated with improvement of major depression treated with pharmacotherapy (prefrontal cortex, left anterior cingulate gyrus, left temporal lobe)^{7,8)} and brain regions which have been reported to be associated with alexithymia (frontocingulate cortex, anterior cingulate cortex, insula, posterior cingulate cortex, medial prefrontal cortex, parietal cortex, premotor cortex)¹⁸⁾ are different although they have considerable overlap. In other words, alexithymic patients might have both different and common impairment of the neural networks com-

pared with the ones which are associated with improvement of major depression treated with pharmacotherapy. This might be one reason of poor response to pharmacotherapy in alexithymic patients with major depression.

The studies that investigated whether alexithymia is a factor that can predict the prognosis of depressive disorder or depressive state are very scarce. In one study¹⁹⁾, 230 outpatients receiving chronic hemodialysis (HD) therapy completed the Beck Depression Inventory-II (BDI-II), the TAS-20, and two subscales of the Social Support Questionnaire. The BDI-II was readministered after a 6-month interval. Deterioration of depression after 6 months was predicted by the presence of alexithymia and poor available support. Our present findings support the Kojima study's contention that alexithymia is one of the predictive factors for the deterioration of depression. Moreover, our findings suggest that alexithymia might hinder the pharmacotherapeutic outcome of major depression in the adjustment to work.

To our surprise, unmarried state was correlated with being at work at 6 months after hospitalization in the patients with major depression. In other words, married state was correlated with not being at work in this population. It is well known that discord within families or within couples worsens the prognosis of depression²⁰⁾. Thus, this result was unexpected. In the present study, the reason why married status was related to not being at work is not known, in part because the details of the patients' family functioning were not investigated. Another study that includes the assessment of the patients' families is needed.

2. Predictors for readmission

No factor was significantly associated with readmission during the 6-month post-discharge period in the participants with major depression.

The recurrence of major depression was reported to be associated with bipolarity²¹⁾. Personality traits other than alexithymia, e.g., neuroticism²²⁾ and social support (e.g., family function²⁰⁾ are also known as predictors for the prognosis of major depression. Further studies including these factors are necessary to identify the predictive factors associated with readmission in patients with major depression.

3. Suggestion for treatment

Alexithymia has been assumed to be negatively associated with psychotherapeutic outcome. Although few empirical studies have examined this issue, recently some studies investigated whether alexithymia really hinder the psychotherapeutic outcome.

In Grabe's study, alexithymic and nonalexithymic inpatients were treated with psychodynamic group therapy. After the treatment, alexithymic patients suffered from higher psychopathological distress at discharge than nonalexithymics²³⁾. Ogrodniczuk reviewed findings from a series of studies that examined the effect of alexithymia on various aspects of the psychotherapeutic enterprise. Alexithymia was associated with poor outcome in both traditional psychodynamic psychotherapy and supportive therapy²⁴⁾.

On the other hand, different findings were reported in cognitive behavior therapy studies. Fifty-five consecutive outpatients with panic disorder received short-term cognitive-behavioral group therapy (CBGT) and were followed up 6 months later. CBGT outcome does not appear to be negatively affected by alexithymia²⁵⁾. Rufer also conducted a prospective study with 42 inpatients with obsessive-compulsive disorder (OCD) receiving intensive, multimodal cognitive-behavioral therapy (CBT). Alexithymia scores did not predict response to multimodal CBT in the OCD patients²⁶⁾. A total of 201 participants with sub-

threshold depression were treated with cognitive behaviour therapy and were followed up for 1 year. Baseline alexithymia scores were not correlated with treatment outcome²⁷⁾. Furthermore, in the study of one hundred alcohol-dependent inpatients, High alexithymic patients did benefit equally from inpatient CBT-like treatment as low alexithymic patients²⁸⁾.

Thus, although the traditional assumption about poor psychotherapeutic outcome in alexithymic patients may fit the case of psychodynamic psychotherapy or supportive therapy, it might not fit the case of cognitive behaviour therapy. It is consistent with this study's outcome because our patients were treated with pharmacotherapy and supportive therapy. Therefore, it might be useful to add cognitive behaviour therapy to pharmacotherapy for alexithymic major depression patients who are resistant to pharmacotherapy.

There are several limitations to this study. First, because the sample size of participants was small, other important factors related to patient prognosis regarding work and readmission may have been overlooked. For example, family history tended to be correlated with readmission during the 6-month post-discharge period in the patients with major depression in the univariate analysis but not in the logistic regression analysis. Second, other factors not assessed in this study might be correlated with prognosis regarding work and readmission (e.g., other personality characteristics or social support issues). Finally, because TAS-20 was administered only once at baseline, whether alexithymic features measured in this study have state or trait characteristics is unknown. However, a longitudinal study of major depression patients revealed that alexithymia scores at baseline correlated significantly with alexithymia scores at follow-up, and suggested that alexithymia has trait characteristics in this population^{29, 30)}.

In conclusion, the present findings suggested that alexithymia might be associated with the 6-month prognosis regarding work state in patients with major depression treated with pharmacotherapy. It has been noted that the DSM-IV(-TR) diagnosis of major depression has heterogeneous characteristics^{31, 32)}, so it might be useful to take care in putting alexithymia into perspective when we intervene to improve the prognosis of work state in patients with major depression. Although the present study has several limitations, its results are meaningful as a first report demonstrating that alexithymia might hinder the pharmacotherapeutic outcome of major depression. We also suggested cognitive behaviour therapy may be useful for these alexithymic patients according to recent literature of alexithymia. In future studies, a detailed investigation of personality characteristics such as alexithymia is needed in order to formulate strategies to improve the prognosis of patients with major depression.

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アレキシサイミアが大うつ病患者の予後に及ぼす影響に関する研究

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【要約】 背景：アレキシサイミアは精神療法の予後を悪化させることが報告されてきた。しかし、アレキシサイミアが薬物療法の予後に与える影響については知られていない。

方法：大うつ病の入院患者 26 名について前方視的に調査した。患者は通常の臨床設定で薬物療法を受けた。入院時に種々の社会医学的項目と TAS-20, SDS を、退院 6 カ月後に就労の有無と再入院の有無を調査した。

結果：ロジスティック回帰分析の結果、退院 6 カ月後の就労の有無に影響を与える有意な因子は、入院時のアレキシサイミアの程度と婚姻の有無だった。再入院の有無に影響を与える有意な因子は存在しなかった。

結論：本研究では、アレキシサイミアは薬物療法を受けた大うつ病患者の予後と関連していた。大うつ病患者の予後を改善するために、アレキシサイミアを考慮した治療戦略を検討することが有用かもしれない。

キーワード：アレキシサイミア, 大うつ病, 予後, 薬物療法