〈Brief Note〉

Correlation between blood biomarkers and depression and anxiety scales in apparently healthy individuals

Kazumasa Isobe[1], Tomoko Ishizu[1], Hitoshi Oikawa[2], Takashi Kamimaki[2],
Michikuni Ishijima[2], Toru Nanmoku[2],
Yasushi Kawakami[1] and Shinichiro Sasahara[3]

Summary Aim The purpose of this study was to assess the correlations between blood biomarkers and depression and anxiety scores in apparently healthy individuals.

Methods The Beck Depression Inventory (BDI) and State-Trait Anxiety Inventories (STAI) 1 and 2 were administered to a total of 120 research participants. A blood sample was also obtained from each participant for measurements of biomarkers (serotonin, brain-derived neurotrophic factor [BDNF], high-sensitivity C-reactive protein [hsCRP], zinc, and folic acid). The Pearson moment correlation was used to determine correlations among the quantitative variables.

Results A significant linear correlation between the BDI and STAI scores was found in all participants. An inverse linear correlation between the BDI score and folic acid was found in all participants (Pearson $r = -0.206$; $P < .05$). The STAI 2 score and folic acid were also inversely correlated (Pearson $r = -0.292$; $P < .01$), as were the STAI 1 score and BDNF (Pearson $r = -0.234$; $P < .05$).

Conclusion Folic acid levels and BDNF levels may be useful for evaluating mental health status in apparently healthy individuals.

Key words: Beck Depression Inventory, State-Trait Anxiety Inventory, Serotonin, BDNF, hsCRP, Zinc

1. Introduction

Depression is a psychiatric disorder with high morbidity and mortality. The World Health Organization predicts that by the year 2020, depression will be the second most important cause of human disability-adjusted life years[1]. In Japan, it is estimated that about 30,000 people commit suicide every year and about half of those individuals seem to have symptoms of depression.

The Beck Depression Inventory (BDI) is a 21-question multiple-choice self-report inventory, one

[1]Department of Laboratory Medicine, University of Tsukuba, Tsukuba, Japan;

[2]Division of Laboratory, University of Tsukuba Hospital, Tsukuba, Japan

[3]Department of Occupational Psychiatry, University of Tsukuba, Tsukuba, Japan

of the most widely used instruments for measuring the severity of depression. The State-Trait Anxiety Inventory (STAI) is a psychological inventory based on a 4-point Likert scale and consists of 40 questions on a self-report basis. The STAI measures two types of anxiety-state anxiety, or anxiety about an event, and trait anxiety, or anxiety level as a personal characteristic.

Several biomarkers were reported to decrease or increase in depression. Serotonin is closely linked to the most recent biochemical hypothesis of depression. Whole blood serotonin was reported to be reduced in patients with major depression[2]. Brain-derived neurotrophic factor (BDNF) is a dimeric protein associated with depression. Serum BDNF levels are also abnormally low in patients with major depression[3].

Moderately elevated levels of high-sensitivity C-reactive protein (hsCRP) in serum have become a well-established marker of low-grade inflammation. Such an increase in hsCRP has also been consistently observed in individuals with depression[4].

Nutritional deficiencies such as zinc[5] or folic acid could theoretically have an influence on brain structure and function, including mood.

In this study, we assessed the relationships between blood biomarkers and mental health scores in apparently healthy men and women.

2. Methods

1) Research participants

We recruited 120 healthy volunteers (43 men and 77 women, aged 21-68 years; average age, 41.9 ± 13.1 and 40.2 ± 11.2 years, respectively) who had no physical signs of disease and were not taking any medications. The participants were employees of Tsukuba University Hospital. At entry, all participants provided written informed consent to participate in the study. The data was collected from January through September 2013 and analyzed in August 2013.

The study protocol was approved by the ethics committee of Tsukuba University Hospital (H24-77).

2) Depression and anxiety scoring

BDI is used for measuring the severity of depression, and STAI is used for measuring two types of anxiety-state anxiety and trait anxiety.

3) Biomarker measurements

Peripheral venous blood samples were collected at around 5 PM into tubes containing EDTA or serum separator gel. Serotonin was determined in EDTA whole blood, using high-performance liquid chromatography (HPLC), as described by Keating et al. Lysed red cell ghosts were centrifuged down at 2000g for 15 minutes before the HPLC analysis[7]. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer⌐s instructions (Promega, USA). hsCRP serum levels were measured using the latex-enhanced immunoturbidimetric method on a nephelometric analyzer. Folic acid levels were measured using a chemiluminescence assay (Siemens Healthcare, Japan). Zinc levels were measured using the colorimetric method (Shino test, Japan) with an automated analyzer (Hitachi 7700, Japan).

4) Statistical analysis

The Pearson product moment correlation was used to determine correlations among the quantitative variables (IBM statistics, SPSS 21.0J).

3. Results

1) Depression and anxiety scores

The mean BDI score was 8.7 ± 5.9; one-third of the participants (43/120) yielded scores higher than 11 (mild depression). The mean STAI1 score was 43.8 ± 10.6 and was significantly correlated with age (Pearson $r = -0.261$; $P < .01$). The mean STAI2 score was 45.4 ± 10.1; one-third of the participants (38/120) yielded scores higher than level 4 (moderate anxiety).

2) Blood biomarkers

The mean serotonin level was 128.5 ± 57.2 ng/mL; neither significant sex difference nor age-dependency was observed. Of the 120 subjects,the serotonin levels of 11 cases were below the lower reference value (53 ng/mL), while those of 21 cases

Table 1   Correlations among BDI, STAI, serotonin, BDNF, hsCRP, Zinc and folic acid.

	BDI	STAI 1	STAI 2	serotonin	BDNF	hsCRP	Zinc
STAI 1	0.410[b]						
STAI 2	0.566[b]	0.838[b]					
Serotonin (ng/mL)	-0.016	-0.038	-0.069				
BDNF (pg/mL)	-0.073	-0.234*	-0.187*	0.234[a]			
hsCRP (mg/dL)	0.056	-0.044	0.002	-0.032	0.045		
Zinc (μ g/dL)	-0.069	-0.051	-0.046	-0.091	-0.034	0.040	
folic acid (ng/mL)	-0.206*	-0.207*	-0.292*	0.086	0.191	0.043	-0.123

Abbreviations: BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; BDNF, brain-derived neurotrophic factor; hsCRP, high-sensitivity C-reactive protein
[a]$P < 0.05$; [b]$P < 0.01$

were above the upper reference value (200 ng/mL). The mean BDNF level was 3336 ± 1271 pg/mL. The BDNF level was significantly correlated with age ($P < .05$). The mean hsCRP level was 0.06 ± 0.09 mg/dL; one-third of the participants (39/120) yielded levels above the normal range (0.04 mg/dL). The mean zinc level was 73.5 ± 11.0 μ g/dL; the level in men was higher than that in women (76.4 vs 71.8; $P =$ .06). The mean folic acid level was 7.9 ± 3.0 ng/mL; the level in women was significantly higher than that in men (8.5 vs 6.8; $P < .01$). The folic acid levels of 2 cases were below the lower reference value (3.6 ng/mL), while those of 6 cases were above the upper reference value (12.9 ng/mL).

3) Correlations between mental health scores and biomarkers

Correlations between the mental health scores and biomarkers are summarized in Table 1. A significant linear correlation between the BDI and STAI scores was found in all participants. An inverse linear correlation between the BDI score and folic acid was found in all participants (Pearson $r = -0.206$; $P < .05$). The STAI 2 score and folic acid were also inversely correlated (Pearson $r = -0.292$; $P < .01$), as were the STAI 1 score and BDNF (Pearson $r = -0.234$; $P < .05$).

4. Discussion

In the present study, we scored BDI and STAI, and measured serotonin, BDNF, hsCRP, zinc, and folic acid levels in 120 apparently healthy individuals. Even though apparently healthy, one-third of the participants showed high levels of depression or anxiety. Only the folic acid levels had a significantly inverse association with the BDI scores. The folic acid levels also had a more significant inverse association with the STAI 2 scores.

Lazarou et al reported on the correlation between folic acid deficiency and depression and the role of folic acid in the treatment of depression[8]. Zhao et al also reported that the prevalence and likelihood of taking folic acid and vitamin supplements varied substantially according to whether the patient had a history of diagnosed depression and anxiety[9]. On the other hand, Christensen et al reported no clear potentiation of antidepressant medication effects by folic acid or vitamin B$_{12}$[10]. Folic acid is considered essential for the functioning of the nervous system. Even though the effect varies substantially, folic acid seems to be associated with depression and anxiety.

The BDNF levels also had a significantly inverse association with the STAI 1 scores. Minelli et al reported a significant correlation between high scores of harm avoidance and low BDNF serum concentrations[11]. Thus, BDNF concentrations may represent a biochemical marker associated with anxiety.

Recently, it was reported that zinc levels were correlated with depression scales in young female students in Iran[12]. However, in the present study, the zinc levels and depression scores were not significantly correlated. In Japan, cases of zinc deficiency may be rare, particularly in apparently healthy individuals.

Even though apparently healthy, one-fourth of the participants showed high levels of hsCRP, indicating the presence of some kind of inflammation as we previously reported[13]. However, the causes of inflammation are so diverse that it is hard to identify depression by measurement of the hsCRP level alone. The reasons for low serotonin levels are also diverse, indicating personal difference. Cleare reported no correlation between low serotonin levels and the degree of depression[2]. Ninety-nine percent of whole blood serotonin is thought to be platelet serotonin content. Even though the mechanisms of serotonin uptake and release are very similar in platelets and neurons, the peripheral concentration of serotonin hardly accounts for its central concentration. Cocci et al reported that the dynamics of platelet membrane viscosity account for the diversity[14].

In conclusion, some blood biomarkers may be useful for evaluating mental health status in apparently healthy individuals.

Conflicts of Interest

There are no conflicts of interest associated with this manuscript.

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