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Decreased serum levels of polyunsaturated fatty acids and folate, but not brain-derived neurotrophic factor, in childhood and adolescent females with depression



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ABSTRACT

Evidence from observational studies suggests that there is an association among depression and brain-derived neurotrophic factor (BDNF), polyunsaturated fatty acids (PUFAs), and folate; however, this association has yet to be examined in childhood and adolescent depression. The objective was to determine whether the BDNF, PUFAs, and folate in serum differ between first-episode childhood and adolescent depressed patients and healthy controls. We measured the serum levels of BDNF, PUFAs, and folate of cases admitted to the hospital for depression ($n=24$) and compared it to that of controls ($n=26$). Subjects and their parents were informed about the nature and the purpose of this study, and a consent form was signed by parents. The ethics committee of Hirosaki University Graduate School of Medicine approved the study protocol. There were significant differences in the docosahexanoic acid (DHA), arachidonic acid (AA), and folate levels between cases and controls. Serum levels of DHA, AA, and folate levels in the patients group were statistically lower than those in the control group, while serum levels of BDNF were not different between cases and controls. These results are in line with findings of previous studies involving adult and elderly subjects, demonstrating lower levels of PUFAs and folate in patients with depression than healthy controls. However, further studies using larger sample size are warranted.

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1. Introduction

Childhood and adolescent depression is a chronic and serious illness that can result in marked functional impairment of the human biological system. It has also been shown that depression in adults has its roots in childhood and adolescence (Birmaher et al., 1996; Weissman et al., 1999; Danese et al., 2008). Recently, there have been reported many studies on understanding the role of different laboratory parameters such as inflammatory markers, brain derived neurotrophic factor (BDNF), and nutritional factors, to elucidate the underlying pathophysiology of depression in adults (Lang and Borgwardt, 2013). However, similar studies in childhood and adolescent depression are a few.

Accumulating evidence suggests that BDNF plays an important role in the pathophysiology of depression, as well as in the mechanisms underlying the therapeutic actions of antidepressants (Duman et al., 1997; Altar, 1999; Nestler et al., 2002; Hashimoto et al., 2004; Martinowich et al., 2007; Hashimoto, 2010). Several studies including meta-analyses reported that the serum BDNF levels in adult patients

with depression were significantly lower serum levels of BDNF than healthy control, and increased after antidepressant treatment (Shimizu et al., 2003; Sen et al., 2008; Brunoni et al., 2008; Bocchio-Chiavetto et al., 2010; Molendijk et al., 2011; Yoshida et al., 2012). Therefore, it is likely that the serum BDNF levels would be a potential biomarker for depression. In the studies intended for adolescent or pediatric depressed patients, there are a few studies examining the serum BDNF levels. Pallavi et al. (2013) reported that adolescent patients with depression had significantly lower levels of BDNF. Sasaki et al. (2011) also reported that serum levels of BDNF in male pediatric patients with depression were significantly lower than those in the male control group. However, there is still not enough information about the serum BDNF in adolescent depression.

Polyunsaturated fatty acids (PUFAs) are essential fatty acids, and classified mainly into omega-3 and omega-6 groups. In animals, dietary omega-3 PUFAs deficiency alters brain chemistry, development and neurotransmission (Das, 2003; De la Presa Owens and Innis, 1999). In clinical, some studies including meta-analyze reported that low blood levels of omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), and omega-6 fatty acids arachidonic acid (AA) are associated with depression in adults (Edwards et al., 1998; Maes et al., 1999; Mamelakis et al., 2002; De Vriese et al., 2003; Su et al., 2003; Freeman et al., 2006; Dinan et al., 2009). In addition,

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the blood omega-6 to omega-3 PUFA ratio has been found to be higher in depressed patients compared to controls (Maes et al., 1996; Riemer et al., 2010). However, not all studies have shown decreased omega-3 PUFA in depressed patients as opposed to healthy subjects (Ellis and Sanders, 1977; Fehily et al., 1981). Mamalakis et al. (2004) reported that the Beck Depression Scale (BDI) was negatively associated with EPA, while the Center for Epidemiologic Studies Depression Scale (CES-D) was positively associated with dihomo-gamma linolenic acid (DGLA) in adipose tissue of adolescent depression. In addition, Pottala et al. (2012) reported that the red blood cell of DHA was inversely associated with depression in adolescent, but this is not a consistent finding (Crowe et al., 2007).

Folate is involved in the metabolism of monoamines like serotonin in the brain (Bottiglieri, 2005) and thus may be related to mood disorder. Several (Morris et al., 2003; Lerner et al., 2006; Kim et al., 2008; Beydoun et al., 2010; Nanri et al., 2012) but not all (Penninx et al., 2000; Tiemeier et al., 2002) observational studies have reported an inverse association between blood folate concentrations and depressive symptoms in middle age or elderly. Furthermore, Murakami et al. (2010) reported that higher intake of dietary folate and vitamin B-6 is independently associated with lower prevalence of depressive symptoms in healthy early adolescent, whereas Fulkerson et al. (2004) found no association between depressed symptoms and folate.

Almost all previous studies have been conducted in adults or elderly, particularly depressive symptoms and serum BDNF and folate levels, therefore, we examined a case-control study comparing serum PUFAs, folate, and BDNF levels in 28 childhood and adolescent patients with depression and 24 healthy controls.

2. Subjects and methods

Twenty-four female patients with childhood and adolescent depression were recruited from Hirosaki University Hospital. All patients who applied to our outpatient clinic and diagnosed as major depressive disorder according to the DSM-IV criteria (American Psychiatric Association, 1994) were included in this study. Patients' ages range between 11 and 19 years. Depression level was assessed through the use of the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) and the Depression Self Rating Scale for Children (DSRSC) (Birleson, 1981). Exclusion criteria consisted of the presence of other major axis I disorders, including schizophrenia, bipolar disorders, anxiety disorders, substance-related disorders and eating disorders, pervasive developmental disorder, as well as the presence of any physical disorders and/or exposure to any drug including antidepressants. It was the first episode of all patients. All the subjects were antidepressant naive. For this reason, they were not subjected to a drug washout.

We applied a group matching for gender age from control group. Twenty six subjects were chosen as the control group, and underwent a comprehensive assessment of medical history to eliminate individuals with any neurological or other medical disorders by Structured Clinical Interview. None of the control subjects initially recruited was found to fulfill these exclusion criteria.

The ethics committee of Hirosaki University Graduate School of Medicine approved the study protocol, and all of the subjects and their parents provided written informed consent for participation in the study.

Serum samples from the patients and normal control subjects were collected and allowed to clot for 30 min, before the centrifugation for 15 min at approximately 3000 rpm. The serum was stored at -80°C until they were used for the assay.

Serum levels of BDNF, polyunsaturated fatty acid, and folate were measured by using the quantitative sandwich enzyme immunoassay (ELISA) (Quantikine kit; R&D Systems), gas-chromatograph (GC-2010; Shimadzu Corporation), and chemiluminescence enzyme immunoassay (CLEIA) (Access folate; Beckman Coulter) according to the manufacturer's instructions, respectively.

The statistical analysis of the two groups was performed using Student's *t*-test. A *p* value less than 0.05 was regarded as statistically significant. All of the analyses were performed using SPSS 18.0J for windows (SPSS Japan Inc., Tokyo, Japan).

3. Results

Demographic and clinical characteristics of the patients and healthy control group are compiled in Table 1. The distribution of

Table 1

Demographic characteristics and serum BDNF, unsaturated fatty acid, and folic acid in adolescent depression patients vs. healthy controls.

Variables	Depression patients (<i>n</i> =24)	Healthy control (<i>n</i> =26)	<i>t</i> -Value	<i>p</i> -Value
Age (year)	16.0 ± 2.2	17.2 ± 2.4	1.8	0.075
BMI (kg/m ²)	20.8 ± 3.4	20.0 ± 2.8	-0.9	0.386
BDI-II score	29.7 ± 13.1	-	-	-
DSRSC score	23.3 ± 6.0	-	-	-
BDNF	20,642 ± 4916	18,885 ± 4076	1.4	0.174
DGLA	27.5 ± 10.5	31.2 ± 9.6	-1.3	0.190
AA (C20:4 <i>n</i> -6)	133.5 ± 27.8	166.9 ± 31.7	-3.9	< 0.001
EPA (C22:5 <i>n</i> -3)	24.1 ± 12.7	27.3 ± 15.3	-0.8	0.435
EPA/AA ratio	0.18 ± 0.09	0.17 ± 0.10	0.5	0.629
DHA	63.1 ± 14.5	79.0 ± 17.4	-3.5	0.001
Folate	3.0 ± 1.6	4.4 ± 2.0	-2.7	0.010

n=Number of subjects. Values are expressed as Mean ± S.D.

BMI: body mass index. BDI-II: Beck Depression Inventory-II. DSRSC: Depression Self Rating Scale for Children. BDNF: brain-derived neurotrophic factor. DGLA: dihomo-gamma linolenic acid. AA: arachidonic acid. EPA: eicosapentaenoic acid. DHA: docosahexanoic acid.

age and body mass index (BMI) was similar amongst patients and the controls. Either in patients or control groups, PUFAs, folate and BDNF levels were not correlated with age, BMI, respectively. There was no correlation among PUFAs, folate, and BDNF levels and the BDI-II or DSRSC scores in patient groups. The DHA, AA, and folate levels in the patients group were statistically lower than those in the control group (*p* < 0.001, *p*=0.001, and *p*=0.01, respectively). Serum BDNF was not different in patients and control groups.

4. Discussion

The primary finding of this study is that childhood and adolescent patients with depression have lower serum AA, DHA, and folate than normal controls, although we did not observe significant difference between patients and controls in serum BDNF levels. In addition, other PUFAs levels of patients, for example, DGLA and EPA levels had also tendency to reduce overall. These findings parallel results of previous studies, which adult and elderly patients with depression have lower serum PUFAs and folate levels than controls (Edwards et al., 1998; Maes et al., 1999; Mamalakis et al., 2002; De Vriese et al., 2003; Freeman et al., 2006; Su et al., 2003; Morris et al., 2003; Lerner et al., 2006; Kim et al., 2008; Dinan et al., 2009; Beydoun et al., 2010; Nanri et al., 2012). In spite of almost the same BMI between patients and controls, however, our results showed patients with depression had a serum PUFAs and folate levels lower than control groups. That is, childhood and adolescent patients with depression might have a lack of nutrition or poor diet. Rao et al. (2008) reported that depressed people make poor food choices and selecting foods, skipping meals, and dominant desire for sweet foods that might actually contribute to depression. However, it is not clear yet whether poor nutrition, as a symptom of depression, causes PUFAs and folate deficiency or a primary PUFAs and folate deficiency produces depression and symptoms in this study.

We however did not find significant difference on serum BDNF levels between patients and controls. Sasaki et al. (2011) reported serum levels of BDNF in Japanese male pediatric patients with depression were significantly lower than those in the male controls but not in females, consistent with our data. By contrast, there is previous evidence that both male and female adolescent patients with depression had significantly lower levels of serum BDNF compared to controls (Pallavi et al., 2013). Although reports on the serum levels of BDNF from a research targeted at adult or elderly patients can also be seen much, detailed reports of measuring serum levels of BDNF in childhood and adolescent depressed patients are

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