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Research Paper

Omega-3 fatty acids related to cognitive impairment in patients with schizophrenia

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ABSTRACT

Cognitive impairment is strongly associated with functional outcome in patients with schizophrenia but its pathophysiology remains largely unclear. Involvement of omega-3 fatty acids in the cognitive function of healthy individuals and patients with neuropsychiatric disease has received increasing attention. The aim of this study was to examine the relationship between omega-3 fatty acids with cognitive function, social function, and psychiatric symptoms in patients with schizophrenia. The subjects included 30 patients with schizophrenia or schizoaffective disorder. Psychiatric symptoms, cognitive function, and social function were assessed using the Positive and Negative Syndrome Scale, the Brief Assessment of Cognition in Schizophrenia (BACS), and the Social Functioning Scale (SFS), respectively. Blood serum omega-3 fatty acids were assessed using gas chromatography. The BACS composite score was significantly correlated with blood eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels. In addition, a daily dose of antipsychotic medication was negatively and significantly correlated with the blood DHA level and with the BACS composite score. Step-wise multiple regression analyses demonstrated that the SFS score was significantly associated with the BACS composite score. Our results indicate that reduced blood omega-3 fatty acids are associated with cognitive impairment, which then impacts social functioning outcomes in schizophrenia.

1. Introduction

Schizophrenia is a chronic disorder characterized by positive symptoms, negative symptoms, and cognitive impairment (van Os and Kapur, 2009). Cognitive function is strongly associated with functional outcome in patients (Domingo et al., 2015; Green and Harvey, 2014; Fett et al., 2011) but the pathophysiology of cognitive impairment in schizophrenia remains largely unclear (Green and Harvey, 2014).

Omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) reportedly have neuroprotective effects via mechanisms such as suppression of inflammation, regulation of neurogenesis, and protection against oxidative stress (Dyall, 2015; Hashimoto et al., 2014). Previous studies found that intake of omega-3 fatty acids improved cognitive performance in rats (Cutuli et al., 2014; Hajjar et al., 2012). Further, a meta-analysis reported that supplementation of omega-3 fatty acids improved episodic memory in adults with mild memory complaints (Yurko-Mauro et al., 2015).

Some meta-analyses of schizophrenia have reported reduced levels of omega-3 fatty acids in the blood (van der Kemp et al., 2012; Hoen et al., 2013). A postmortem study found lower omega-3 fatty acid concentrations in the brain (McNamara et al., 2007). Associations between omega-3 fatty acids and psychiatric symptoms have been reported in schizophrenia (Arvindakshan et al., 2003; Bentsen et al., 2012; Sethom et al., 2010; Solberg et al., 2015; Watari et al., 2010), but few studies have investigated the involvement of omega-3 fatty acids in the pathophysiology of cognitive impairment. Therefore, the current study aimed to clarify the relationship between omega-3 fatty acids with cognitive function, social function, and psychiatric symptoms in patients with schizophrenia.

2. Methods

2.1. Subjects

The subjects were 30 patients with schizophrenia or schizoaffective disorder, diagnosed according to DSM-5 (Table 1). Six of them were inpatients and their average hospitalization period was 72.83 (standard deviation = 35.06) days. All patients were being treated with antipsychotic medication. The equivalent daily dose of antipsychotic medication was calculated using the psychotropic dose equivalency tables for Japan (Inada and Inagaki, 2015). Two patients were

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Table 1
Demographic and clinical characteristics of patients.

Measure, $N = 30$	Mean	SD
Gender (male/female)	12/18	
Age (years)	45.25	11.98
Duration of illness (years)	18.45	9.97
Education (years)	13.20	2.26
GAF	49.33	8.14
PANSS total score	72.50	11.07
PANSS positive score	16.37	4.40
PANSS negative score	19.30	4.18
PANSS general psychopathology score	37.17	5.30
BACS composite score	− 1.93	1.29
SFS total score	109.60	32.00
Chlorpromazine equivalent dose (mg/day)	591.42	275.06
DHLA (μg/mL)	41.10	11.83
AA (μg/mL)	180.16	46.85
EPA (μg/mL)	47.53	25.93
DHA (μg/mL)	122.72	42.90
BMI (kg/m^2)	23.88	3.90
Systolic BP (mm Hg)	126.37	18.29
Diastolic BP (mm Hg)	80.57	11.83
Total cholesterol (mg/dL)	190.43	39.29
HDL cholesterol (mg/dL)	48.23	12.30
LDL cholesterol (mg/dL)	113.83	29.08
Triglycerides (mg/dL)	130.93	98.76
Glucose (mg/dL)	96.30	21.29
HbA1c (%)	5.68	0.68

GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; BACS, Brief Assessment of Cognition in Schizophrenia; SFS, Social Functioning Scale; DHLA, dihomo-γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c.

prescribed antihypertensive drugs, and other 2 patients were received hypoglycemic agent. This study was approved by the Wakayama Medical University Ethics Committee, and written informed consent was obtained from all subjects.

2.2. Assessment

The subjects underwent assessment of psychiatric symptoms, cognitive function, and social function using the Positive and Negative Syndrome Scale (PANSS); the Brief Assessment of Cognition in Schizophrenia (BACS) Japanese version (Kaneda et al., 2007); and the Social Functioning Scale (SFS) Japanese version (Nemoto et al., 2008), respectively. In the BACS, z-scores were calculated for each subcomponent score using a healthy Japanese population dataset (Kaneda et al., 2013); the composite score was calculated by averaging the z-scores of the six subcomponents. Blood samples were collected after overnight fasting. The blood biochemistry tests included total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides (TG), glucose, and hemoglobin A1c (HbA1c). Blood serum polyunsaturated fatty acids were assessed as dihomo-gamma-linolenic acid, arachidonic acid, EPA, and DHA using gas chromatography.

2.3. Data analysis

Correlations among each blood polyunsaturated fatty acid value, the BACS composite score, each PANSS score (positive, negative, global psychopathological, total), the SFS score, and daily dose of antipsychotic medication were analyzed using Spearman's rank correlation test. Correlations among each blood polyunsaturated fatty acid value, TG, total cholesterol, HDL cholesterol, LDL cholesterol were analyzed using Spearman's rank correlation test. Step-wise multiple regression analysis was used to reveal the effect of cognitive function, psychiatric symptoms, and antipsychotic medication on social function. The SFS score was entered as a dependent variable and the BACS composite score, each PANSS score, and the daily dose of antipsychotic medication were entered as independent variables. The level of statistical significance was set at $p < 0.01$ for Spearman's correlation tests and at $p < 0.05$ for the step-wise multiple regression analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows (IBM Japan, Ltd., Tokyo, Japan).

3. Results

Average values of each blood chemical analysis and of each psychological battery are shown in Table 1. Four patients had both hypertension (systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg, or using of any antihypertensive drugs) and dyslipidemia (HDL cholesterol < 40 mg/dL, or total cholesterol ≥ 240 mm Hg, or TG ≥ 150 mm Hg), 1 patient had both hypertension and diabetes (either Hba1c ≥ 6.5% and fasting glucose ≥ 126 mg/dL, or using of any hypoglycemic agent), 1 patient had both dyslipidemia and diabetes. Three patients had hypertension only, 6 patients had dyslipidemia only, and 1 patient had diabetes only. In the Spearmen's rank correlation analyses, the BACS composite score was significantly correlated with the blood EPA level ($r = 0.474$, $p = 0.008$) and blood DHA level ($r = 0.524$, $p = 0.003$) (Table 2, Fig. 1). In addition, a daily dose of antipsychotic medication was negatively and significantly correlated with the blood DHA level ($r = -0.469$, $p = 0.009$) and the BACS composite score ($r = -0.501$, $p = 0.005$) (Table 2). Total cholesterol was significantly

Table 2
Spearman's correlations among the Positive and Negative Symptom Scale (PANSS), Brief Assessment of Cognition in Schizophrenia (BACS), Social Functioning Scale (SFS), chlorpromazine equivalent dose (CPZ), and polyunsaturated fatty acids.

	PANSST	PANSSP	PANSSN	PANSSG	BACS	SFS	CPZ	DHLA	AA	EPA	DHA
PANSS T	1										
PANSS P	0.653*	1									
PANSS N	0.897*	0.357	1								
PANSS G	0.897*	0.414	0.848*	1							
BACS	− 0.362	− 0.339	− 0.395	− 0.272	1						
SFS	− 0.325	− 0.234	− 0.401	− 0.254	0.505*	1					
CPZ	0.353	0.347	0.331	0.277	− 0.501*	− 0.451	1				
DHLA	− 0.202	− 0.122	− 0.237	− 0.176	0.140	0.350	− 0.264	1			
AA	− 0.158	− 0.053	− 0.274	− 0.245	0.255	0.267	− 0.426	0.473*	1		
EPA	− 0.057	0.129	− 0.222	− 0.153	0.474*	0.242	− 0.362	0.273	0.484*	1	
DHA	0.054	0.192	− 0.088	− 0.031	0.524*	0.280	− 0.469*	0.196	0.481*	0.838*	1

PANSS, Positive and Negative Symptom Scale; T, total score; P, positive score; N, negative score; G, general psychopathology score; BACS, Brief Assessment of Cognition in Schizophrenia composite score; SFS, Social Functioning Scale; CPZ, chlorpromazine equivalent dose; DHLA, dihomo-γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

* $p < 0.01$.

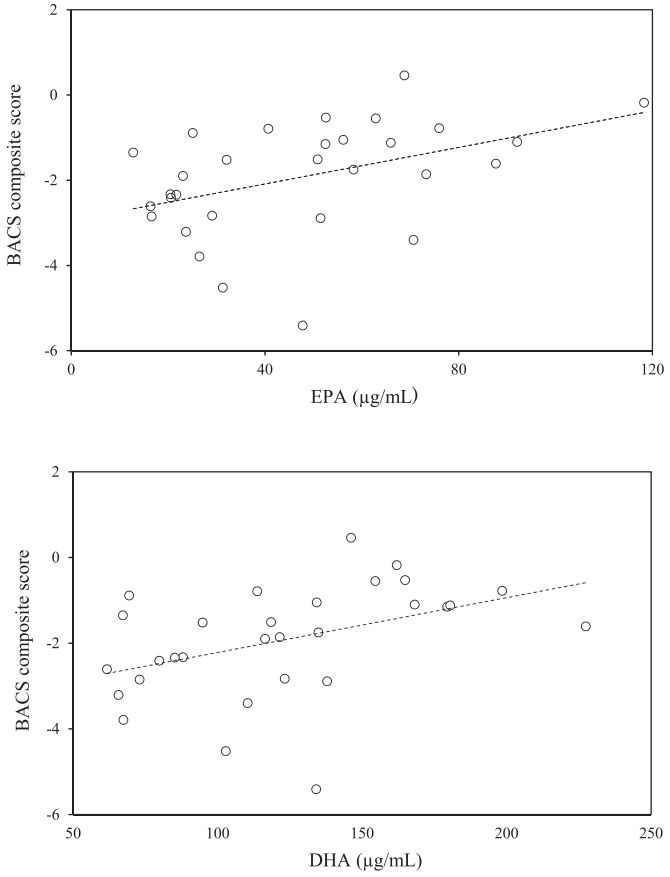

Fig. 1. Scattergram of blood omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) levels and the Brief Assessment of Cognition in Schizophrenia (BACS) composite score in patients with schizophrenia.

Table 3
Step-wise multiple regression analysis of the relationship between the SFS with the PANSS, BACS composite score, and CPZ.

	Standardized coefficient beta	t statistics	*p* value
Constant	—	14.466	0.000
PANSS T	− 0.169	− 0.949	0.351
PANSS P	− 0.101	− 0.579	0.567
PANSS N	− 0.115	− 0.646	0.524
PANSS G	− 0.194	− 1.156	0.258
BACS	0.522	3.238	0.003*
CPZ	− 0.238	− 1.293	0.207

SFS, Social Functioning Scale; PANSS, Positive and Negative Symptom Scale; T, total score; P, positive score; N, negative score; G, general psychopathology score; BACS, Brief Assessment of Cognition in Schizophrenia; CPZ, chlorpromazine equivalent dose.

* $p < 0.05$.

correlated with the blood EPA level ($r = 0.493$, $p = 0.006$) and blood DHA level ($r = 0.497$, $p = 0.005$), and LDL cholesterol was significantly correlated with the blood EPA level ($r = 0.484$, $p = 0.007$). There were no significant correlation between LDL cholesterol and the blood DHA level ($r = 0.458$, $p = 0.011$), between HDL cholesterol and each blood polyunsaturated fatty acid value (EPA; $r = 0.160$, $p = 0.399$, DHA; $r = 0.085$, $p = 0.655$) and between TG and each blood polyunsaturated fatty acid value (EPA; $r = 0.078$, $p = 0.683$, DHA; $r = 0.206$, $p = 0.275$). Step-wise multiple regression analyses revealed that the SFS score was significantly related with the BACS composite score ($\beta = 0.522$, $p = 0.003$) (Table 3).

4. Discussion

This study revealed significant correlations between the blood level of omega-3 fatty acids, BACS composite score, and daily dose of antipsychotic medication in patients with schizophrenia. To our knowledge, the current study is the first to demonstrate a direct association between omega-3 fatty acids and cognitive function as measured by neuropsychological assessment in patients with schizophrenia.

In patients with schizophrenia, the BACS composite score was significantly correlated with the blood EPA and DHA levels and step-wise multiple regression analyses demonstrated that the BACS composite score was significantly associated with the SFS score. Omega-3 fatty acids are important components of cell membranes and the myelin sheath that surrounds axons (Dyall, 2015; Hashimoto et al., 2014). Findings from naturalistic studies and clinical trials in healthy individuals indicate that omega-3 fatty acid intake may be associated with increased functional activation of the prefrontal cortex in children and greater gray matter volume and white matter integrity during aging (Bos et al., 2016). In schizophrenia, Condray et al. (2008) reported that erythrocyte membrane polyunsaturated fatty acids levels were related to the N400, which is an electrophysiological measure of semantic memory and language; however, that previous study did not show a direct relationship between omega-3 fatty acid levels and cognitive function (Condray et al., 2008). In the patients with schizophrenia in the current study, the blood omega-3 fatty acid level was significantly associated with the BACS composite score, and the BACS composite score was significantly associated with the SFS score. These results indicate that reduced omega-3 fatty acids are associated with cognitive impairment, which then impact the patient's social functioning outcomes.

In this study, our finding of a significant negative correlation between a daily dose of antipsychotic medication and the blood DHA level should be interpreted cautiously. Some studies have reported lower omega-3 fatty acid levels in never-medicated relative to medicated patients with schizophrenia (Khan et al., 2002; Arvindakshan et al., 2003). Conversely, a different study found no difference in omega-3 fatty acid levels between medicated and unmedicated schizophrenia patient groups (Solberg et al., 2015). Increased omega-3 fatty acid levels following antipsychotic medication therapy was reported (Evans et al., 2003; Sethom et al., 2010; McEvoy et al., 2013) but it is unclear whether the changes in omega-3 fatty acid levels following medication therapy are a direct result of the medications or a result of improved psychiatric symptoms while medicated (Sethom et al., 2010). Meta-analyses reported a significant reduction in omega-3 fatty acids both in never-medicated and medicated patients with schizophrenia compared with healthy controls (van der Kemp et al., 2012; Hoen et al., 2013), but an antipsychotic medication-induced increase in omega-3 fatty acids was not confirmed (Hoen et al., 2013). To our knowledge, the current study is the first to demonstrate a direct negative linear relationship between a daily dose of antipsychotic medication and omega-3 fatty acid levels. Future longitudinal studies are necessary to investigate the effects of antipsychotic medications on omega-3 fatty acid levels.

We did not find a significant relationship between the omega-3 fatty acid level and PANSS score. Some previous studies reported an association between omega-3 fatty acid levels and psychiatric symptoms. A statistically significant negative correlation was reported between omega-3 fatty acids and negative symptoms in never-medicated (Arvindakshan et al., 2003) and unmedicated (Sethom et al., 2010) patients, and a greater severity of negative symptoms was found in acute-phase patients with low omega-3 fatty acid levels compared with those having high omega-3 fatty acid levels (Bentsen et al., 2012). On the other hand, omega-3 fatty acid levels were significantly positively correlated with negative symptoms in stable chronic patients (Solberg et al., 2015). In a study of Japanese acute phase unmedicated patients with schizophrenia, omega-3 fatty acid levels were negatively

significantly correlated with hostility but not with negative symptoms (Watari et al., 2010). These inconsistent findings among the current and previous studies on the relationship between omega-3 fatty acid levels with psychiatric symptoms may be explained by differences in the severity of psychiatric symptoms, duration of illness, and antipsychotic medication, as well as age, ethnicity, or lifestyle, including diet.

The current study revealed a significant negative correlation between a daily dose of antipsychotic medication and the BACS composite score. A meta-analysis showed that neurocognitive impairment in patients with schizophrenia was substantially affected by a higher dosage of antipsychotic medication (Knowles et al., 2010), and two previous studies showed a significant negative correlation between antipsychotic medication dosage and the BACS composite score (Elie et al., 2010; Hori et al., 2012). In line with these previous studies, our results suggest that a higher dosage of antipsychotic medication may have an adverse impact on cognitive function in patients with schizophrenia.

Finally, this current study showed that the blood level of omega-3 fatty acids was significantly correlated with the total and LDL cholesterol. Our results were in line with the results of Japanese previous studies which showed that higher level of omega-3 fatty acids was associated with increased LDL cholesterol (Nogi et al., 2007; Inoue et al., 2013; Itakura et al., 2012). A meta-analysis reported that omega-3 fatty acid supplements containing both EPA and DHA reduced TG but concomitantly increased LDL cholesterol (Eslick et al., 2009), and intake of omega-3 fatty acids from daily diet might influenced serum lipids metabolism in our subjects.

Limitations of this study include the cross-sectional design and lack of an appropriate control group. Further longitudinal studies are needed to investigate the effect of omega-3 fatty acids on subsequent development of cognitive impairment.

In summary, the current study demonstrated that the blood omega-3 fatty acid level was significantly associated with the BACS composite score and that the BACS composite score was significantly associated with the SFS score in patients with schizophrenia. These results indicate that reduced omega-3 fatty acid levels are associated with cognitive impairment, which then impacts social functioning outcomes in patients with schizophrenia.

Conflict of interest statement

The authors declare no conflicts of interest.

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Contributors

Dr. Satogami and Dr. Takahashi wrote the protocol and conducted the study. Dr. Satogami oversaw subject recruitment. Dr. Satogami performed the initial analyses and wrote the first draft of the paper. Dr. Takahashi assisted additional analyses and writing of the paper. Dr. Yamada, Dr. Ukai and Dr. Shinosaki provided feedback about the study design during study implementation. All authors contributed to and have approved the final manuscript.

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