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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.

* $p < 0.01$.