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Serum Levels of Polyunsaturated Fatty Acids and the Risk of Posttraumatic Stress Disorder

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Recent studies reporting the potential effect of polyunsaturated fatty acids (PUFAs) on neurogenesis suggest that the promotion of neurogenesis could be a promising intervention for preventing posttraumatic stress disorder (PTSD). More specifically, docosahexaenoic acid (DHA) [1] and arachidonic acid (AA) [2] have been shown to promote hippocampal neurogenesis. In the pathogenesis of PTSD, fear memory becomes excessively consolidated. Given that the period of hippocampus-dependent fear memory is longer in mice with decreased hippocampal neurogenesis and shorter in mice with active hippocampal neurogenesis [3], fear memory might be controlled by regulating such neurogenesis.

Omega-3 PUFA supplements containing DHA and eicosapentaenoic acid (EPA) have recently been suggested in an open trial to prevent PTSD [4], and in a randomized trial to attenuate PTSD symptoms in women [5]. In the present study, to examine the hypothesis that omega-3 PUFA supplementation is associated with a reduced risk for PTSD, we conducted a nested case-control analysis of the serum fatty acid composition from 300 antidepressant-naïve, severely injured patients who were participants in the Tachikawa Cohort of Motor Vehicle Accident Study [6].

To examine the potential of serum PUFAs as a biomarker of PTSD after accidental injury, 10-ml blood samples were drawn at baseline. Serum samples were stored at -80°C . The fatty acid composition of the total phospholipid fraction was determined by gas chromatography (GC-2014 Shimadzu Corporation, Kyoto, Japan) with a DB-225 capillary column (0.25 mm, 30 m length i.d., 0.25 μm ; J&M Scientific, Folsom, Calif., USA) as previously described [7].

At the 6-month follow-up, trained psychiatrists administered the Clinician-Administered PTSD Scale in structured interviews to determine if the participants met the criteria for current full-blown or partial PTSD [8]. Participants were deemed to have partial PTSD if they met the criteria for B (re-experiencing) plus either C (avoidance) or D (hyperarousal), or C plus D while meeting the criteria for stressor, duration, and impairment.

Of the total 300 participants, 139 attended the 6-month assessment and 106 completed the interview. Reasons for dropout were

refused to participate in follow-up ($n = 24$), no response to telephone and mail ($n = 126$), moved to an unknown address ($n = 9$), questionnaire data alone ($n = 33$), and exclusion due to serious psychiatric symptoms ($n = 2$). We could obtain serum samples at baseline from 237 participants. We tried to contact missing subjects by postal mail, e-mail, and telephone, distributed several newsletters to maintain response rates, and tried to obtain questionnaire data alone at minimum. Generally, it was very difficult to contact participants, especially those who went back to work. To assess the mechanisms of bias due to dropout, we evaluated intergroup differences between the participants attending the 6-month assessment and those who dropped out. We also considered factors associated with this dropout revealed by our previous study involving the same participants [9]. On this basis, we decided on sex, the Impact of Event Scale-Revised score, the Injury Severity Scale score, subjective loss of consciousness, and education level as potential predictive factors of dropout, and took the missing at random mechanism described by Rubin (cited in Enders [10]) to account for the missing data. As a sensitivity analysis under the missing at random assumption, we performed multiple imputation with potential associative factors to impute PTSD diagnosis at 6 months post-MVA for the participants who dropped out. Multiple imputation was conducted using PROC MI and MIANA-LYZE, SAS 9.1.3 (SAS Institute, Cary, N.C., USA).

Means (expressed as percent total fatty acids) for each peak of AA, EPA, and DHA were calculated for both groups. As age and sex were assumed to be associated with dietary habit, we examined the association between age, sex, and serum levels of AA, EPA, and DHA by Student's *t* test or Pearson's correlation. To estimate the risk for PTSD according to the serum level of PUFAs, we categorized each participant according to tertiles determined from the distribution of fatty acid levels in the control group. We then performed logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals. Multivariate models were sequentially adjusted for age, sex, frequency of alcohol drinking, smoking (current smoker or not), and level of education. The tertile analysis suggested a linear relation, so tests for trend were performed by introducing a continuous variable into the conditional regression model. All analysis was performed using SPSS version 19.0J for Windows (SPSS Inc., Tokyo, Japan). All tests were two-sided, and *p* values of 0.05 or less were considered statistically significant.

At 6 months post-motor vehicle accident, 15 participants met the criteria for current full-blown or partial PTSD [mean age $\pm$ SD, 46.7 ± 16.1 years; women, 8 (53.3%)] and 222 had no PTSD [mean age $\pm$ SD, 36.3 ± 14.9 years; women, 43 (19.4%)]. There were significant differences in age and sex between the two groups. EPA and DHA levels were significantly higher in women than in men [EPA: 2.18 ± 1.06 vs. 1.60 ± 0.86 , $t = 15.9$, $p < 0.001$; DHA: 7.39 ± 1.39 vs. 6.21 ± 1.39 , $t = 28.8$, $p < 0.001$], but there was no significant difference in AA level between the sexes (8.79 ± 1.60 vs. 8.84 ± 1.63 , $t = 0.05$, $p = 0.83$). A significant correlation was found between age

Table 1. Relative risk for PTSD (full-blown PTSD and partial PTSD) at 6 months after motor vehicle accident and serum PUFA level at baseline (n = 237)

	Tertile of PUFAs			p for trend
	1	2	3	
Arachidonic acid				
Mean, %	7.13	8.89	10.69	
Range, %	≤8.17	8.18–9.73	≥9.74	
Case	10/84	4/78	1/75	
OR (95% CI)	1.00	0.51 (0.15–1.8)	0.12 (0.02–1.03)	0.030
OR* (95% CI)	1.00	0.46 (0.13–1.7)	0.12 (0.01–1.01)	0.027
Eicosapentaenoic acid				
Mean, %	0.90	1.50	2.79	
Range, %	≤1.18	1.19–1.91	≥1.92	
Case	6/80	5/79	4/78	
OR (95% CI)	1.00	0.43 (0.11–1.78)	0.15 (0.03–0.74)	0.020
OR* (95% CI)	1.00	0.51 (0.12–2.24)	0.12 (0.02–0.63)	0.011
Docosahexaenoic acid				
Mean, %	4.93	6.31	8.08	
Range, %	≤5.73	5.74–6.91	≥6.92	
Case	3/77	5/79	7/81	
OR (95% CI)	1.00	0.95 (0.30–6.00)	0.68 (0.24–5.28)	0.614
OR* (95% CI)	1.00	0.98 (0.20–4.86)	0.56 (0.10–3.10)	0.450

CI = Confidence interval; OR = odds ratio adjusted for age and sex; OR* = odds ratio adjusted for age, sex, frequency of alcohol drinking, smoking, and level of education.

and each PUFA level (AA: $r = -0.23$, $p < 0.001$; EPA: $r = 0.42$, $p < 0.001$; DHA: $r = 0.47$, $p < 0.001$). There was no significant association between AA, EPA, and DHA levels (data not shown).

AA and EPA levels were significantly inversely related to risk for PTSD (table 1). When compared with participants with AA and EPA levels in the lowest tertile, risk for PTSD was significantly lower among those with levels in the middle (adjusted OR, 0.46; 0.51) and highest (adjusted OR, 0.12; 0.12) tertiles.

We found that the baseline serum levels of AA and EPA were inversely associated with subsequent risk for developing PTSD after accidental injury. The association was linear, with statistically significant inverse trends across tertiles of AA and EPA levels. The finding for EPA is remarkably similar to that reported in a meta-analysis of case-control studies involving depression and EPA [11]. Moreover, a recent meta-analysis of randomized trials showed a significant antidepressant effect of EPA in patients with major depression [12]. The finding for AA also seems to be in line with the results of an animal study suggesting the potential benefit of AA in hippocampal neurogenesis [2]. As no association was found between AA and major depression in a previous study [11], AA level might be specific to PTSD pathology.

The limitations of this study are that the results were obtained from a single institution in Japan and were based on a small sample. That age and sex showed a significant impact on PUFA levels will be important to assess further. The positive correlations found between each of the three PUFAs and age are consistent with the findings of previous reports [13, 14]. The association between

PUFAs and PTSD should now be explored in a well-designed observational study; if the observed association is judged to be causal, intervention trials will then be needed to elucidate causality.

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