

Original Article

The effects of docosahexaenoic acid-rich fish oil on behavior, school attendance rate and malaria infection in school children – a double-blind, randomized, placebo-controlled trial in Lampung, Indonesia

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Background: There are only a very limited number of reports of intervention studies on the effects of fish oil on behavior in normal school children. **Objective:** To observe the effects of fish oil on behavior and school attendance rates in school children. **Design:** Fourth to sixth graders (mostly 9-12 years of age) of an elementary school in Lampung Province, Indonesia, were randomly divided into either a docosahexaenoic acid (DHA) group (n=116) or a control group (n=117) in a double-blind manner. The subjects in the DHA group took 6 fish oil capsules per day (0.65g DHA and 0.10g eicosapentaenoic acid (EPA)/day) for 3 months. Controls took soybean oil capsules. Two questionnaires were administered and blood was taken at the start and end of the study. Two questionnaires were administered at the start and end of the study: Hostility-Aggression Questionnaire for Children (HAQ-C) and Barratt Impulsiveness Scale, version 11 (BIS-11), for measurement of aggression and impulsivity, respectively. Attendance was recorded during the study period. **Outcomes:** The concentrations of DHA and EPA in the phospholipid fraction in red blood cells were significantly increased in the DHA group. Behavior checked with HAQ-C or BIS-11 did not show any differences between groups. However, the odds ratio of inability to attend school regularly during the study period was 0.40 (95%CI: 0.23-0.71) in the DHA group compared with controls ($p=0.002$). **Conclusions:** DHA-rich fish oil may improve the school attendance rate of children in Lampung, Indonesia

Key Words: behavior, fatty acid composition of red blood cells, fish oil, intervention study, malaria, school attendance rate

INTRODUCTION

During the last two decades relationships between n-3 fatty acids and behavior or psychiatric disorders has been intensively investigated. The relationship between those fatty acids and mood disorders is well documented.^{1,2} The effect on aggression or hostility has also been investigated.^{3,4} The mechanism of action of n-3 fatty acids with regard to psychiatric disorders and behavior is not clear, but the most promising target of research is the serotonergic neuron system; activation of the serotonergic neuron system with n-3 fatty acids prevents depression, suicide ideation and aggression; and the reduction of the noradrenergic system with n-3 fatty acids may be important, too.⁴

On the other hand, there is a possibility that n-6 fatty acids may enhance aggression. Hibbeln et al⁵ calculated

linoleic acid available for human consumption for 12 major seed oils in the food supply for the years 1961 to 2000 in 5 Western countries, and also calculated homicide mortality rates. A positive correlation was found between apparent consumption of linoleic acid and homicide mortality across countries and time; within each country there was correlation between greater linoleic acid and homicide mortality over time.⁵

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Manuscript received 24 August 2007. Initial review completed 13 March 2008. Revision accepted 24 April 2008.

In a previous study, we conducted a placebo-controlled, double-blind trial in Japan with 166 healthy school children of 9-12 years of age to investigate effects of docosahexaenoic acid (DHA)-fortified foods on aggression.⁶ It was found that physical aggression in girls assessed by Hostility-Aggression Questionnaire for Children (HAQ-C) increased significantly in the control group and did not change in the DHA-fortified group with a significant inter-group difference. In the control group n-6 fatty acids were increased in the phospholipid fraction in red blood cells (RBCs) after placebo administration, which might explain why physical aggression was increased (see above). Actually there was a highly significant inverse correlation between Δ scores of physical aggression and Δ eicosapentaenoic acid/arachidonic acid (EPA/AA) ratios in the phospholipid fraction in RBCs in girls. Impulsivity was also affected favorably in girls in the DHA-fortified group.⁶ In another intervention study in Thailand with school children as subjects, it was found that school attendance rates were better in the fish oil group.⁷ In the present study, we investigated the effects of fish oil on behavior including school attendance rates in a different setting.

Menhaden fish oil without vitamin E protected mice from malaria.⁸ Pure DHA and eicosapentaenoic acid (EPA) with vitamin E also partially protected mice from malaria.⁹ We, therefore, tried to determine whether fish oil administration decreased clinically apparent sick days from malaria as an independent endpoint.

SUBJECTS AND METHODS

Study protocol

Fourth to sixth graders of an elementary school located in South Lampung District, Lampung Province (Sumatra Island), Indonesia, were invited to participate, and 233 subjects agreed to do so. They were 8-14 years of age (mostly 9-12) at the start of the study. They were stratified according to school grade, and randomly divided into either a DHA group (n=116, 62 boys and 54 girls, 10.6±1.1 years old) or a control group (n=117, 54 boys and 63 girls, 10.6±1.0 years old) in a double-blind manner. All subjects were asked to maintain their physical activity level and consume their habitual diets during the study period of 3 months. Questionnaires were implemented and blood sampling collected at the start and end of the study.

School attendance rates were checked by homeroom teachers. The local health center of South Lampung District and the ethics committees of Hasanuddin University and Toyama Medical and Pharmaceutical University (now, University of Toyama) approved the present study. Written informed consent was obtained from each subject's parent/guardian after full verbal and written explanations.

Capsule administration

The Japanese side (mainly KH) generated the randomization table with blocks of four (2 controls and 2 DHAs), packed capsules in bottles with consecutive numbered labels on them, and sent them to Indonesia. At the school where the study was conducted, three study nurses allocated capsule bottles to children according to their ID numbers under the supervision of the Indonesian researchers (mainly DS), and safely kept the capsule bottles with

subject ID numbers on bottle labels during the study. They handed to all study subjects 6 capsules (210mg oil/capsule) of either DHA-rich fish oil or placebo oil soon after lunch on each school day during the study period. The study participants took the capsules at school. Every Friday the nurses handed an extra 12 capsules to study subjects for the coming Saturday and Sunday and those capsules were consumed at home. The DHA-rich fish oil contained 52% DHA and 8% EPA. Consequently, the daily doses of DHA and EPA in the DHA group were 0.65g and 0.10g, respectively. Soybean oil was used as the control oil, because the cooking oil used on mostly Sumatra Island is soybean oil. The fatty acid composition of the oils is shown in Table 1. Both test oils contained 0.2% α -tocopherol.

Table 1. Ingredients of the two kinds of capsules

	Groups	
	Control	DHA
Fatty acids (mg / 6 capsules)		
	(%)	(%)
16 : 0	132 (10.5)	172 (13.6)
18 : 0	46 (3.7)	43 (3.4)
18 : 1 n-9	313 (24.8)	119 (9.5)
18 : 2 n-6	656 (52.0)	14 (1.1)
18 : 3 n-3	87 (6.9)	ND (ND)
20 : 4 n-6	ND (ND)	39 (3.1)
20 : 5 n-3	ND (ND)	101 (8.0)
22 : 6 n-3	ND (ND)	652 (51.7)

Six capsules containing 1.26g oil were administered per day for 3 months; Both test oils contained 0.2% vitamin E. ND, not detected

Questionnaires

HAQ-C of the Buss-Perry Aggression Questionnaire¹⁰ was translated into Indonesian and used. This questionnaire contains 27 multiple-choice questions [five choices were provided: extremely uncharacteristic of me (point=1), somewhat uncharacteristic of me (=2), neither uncharacteristic nor characteristic of me (=3) somewhat characteristic of me (=4) and extremely characteristic of me (=5)], and each question belongs to one of the following four categories: physical aggression, verbal aggression, anger and hostility. Here are example questions for each category: physical aggression (If somebody hits me, I hit back.), verbal aggression (I can't help getting into arguments when people disagree with me.), anger (Some of my friends think I'm a hothead.) and hostility (At times I feel I have gotten a raw deal out of life.). Impulsivity was measured with Barratt Impulsiveness Scale, version 11 (BIS-11). This questionnaire asks 30 questions about thinking, planning, concentration etc. with multiple choices. These two questionnaires were validated in Asian people^{11,12}, but not in Indonesians yet.

Fatty acid composition of RBCs were washed two times with saline and sent to Japan with dry ice. The samples were kept at -80 °C until fatty acid analysis. The total lipids of RBC (100 μ L) were extracted according to Bligh and Dyer¹³. The total phospholipid fraction separated by thin-layer chromatography was transmethylated and analyzed with a Shimadzu gas-liquid chromatograph GC-14A, equipped with a DB225 capillary column (J&W Scientific Folsom, CA)¹⁴.

Detection of malaria: Thick and thin blood smears were prepared using aseptic finger prick at the start and end of the study. The smears were stained with Giemsa and examined under a light microscope. In addition, the blood smear was collected whenever study nurses suspected that subjects were infected with malaria.

Statistics

After the Indonesian side completed compiling spread sheets of all results, both sides exchanged the randomization table and the spread sheets of results at the same time. The primary endpoint of the present study was the effects of fish oil on behavior; to be more specific, the effects on physical aggression scores in HAQ-C. Power calculation showed that, with 200 school children, the possibility to obtain a significant result was >0.8 in the case that the effect size was small ($d=0.25$). The secondary endpoint was the effects on clinically apparent malaria infection.

Data were analyzed on a basis of intention-to-treat. Unfortunately some data were not collected from subjects either at the start or end of the study (or both) because of the absence of some subjects at those test times (or dates). Also some questionnaires were not well completed, and meaningful results could not be extracted from those questionnaires. With regard to the fatty acids and questionnaire results, only those datasets that were able to be compared between before and after the study were included in the present analysis.

Data are expressed as mean \pm SD. The fatty acid composition of RBCs and behavior were compared between groups by analysis of covariance. Intragroup differences

were compared by the paired t-test. Comparison of malaria detection between groups was performed with χ^2 method. The odds ratios of inability to attend school were calculated by multiple logistic regression analysis. StatView (Japanese version 5; SAS Institute, CA) was used for statistical analyses. $p<0.05$ was considered as significant.

RESULTS

Blood samples could not be taken in 8 and 4 subjects at either the start or end of the study in the control and DHA groups, respectively. The DHA and EPA concentrations in the total phospholipid fraction in RBCs were significantly increased in the DHA group, whereas there were no significant changes in any fatty acids concentrations in the control group (Table 2).

With regard to the HAQ-C questionnaire, data could not be compared between before and after the intervention in 21 and 23 subjects in the control and DHA groups, respectively, mostly because of incompleteness of subjects' answers. There were no significant changes either over time or between groups in any four categories of HAQ-C (Table 3). In the case of BIS-11 questionnaire, 34 control data and 31 DHA data were unable to be compared, mostly because of incomplete answers again. There was no significant difference in BIS-11 scores between groups either (Table 3). The same was true when calculated in each sex in both questionnaires.

In the control group, 49 subjects were absent from school at least once in the study period, whereas 27 subjects were so in the DHA group. The odds ratios of inability to attend school perfectly during the study period in

Table 2. Changes in the fatty acid composition (%) of RBC phospholipids

Fatty acid	Control (n=109)		DHA (n=112)	
	Start	End	Start	End
16:0	27.0 \pm 1.8	26.5 \pm 1.2	27.2 \pm 1.8	26.5 \pm 1.2
18:0	13.7 \pm 1.1	13.2 \pm 0.8	13.6 \pm 1.2	13.3 \pm 0.7
18:1(n-9)	13.4 \pm 0.8	13.6 \pm 0.8	13.4 \pm 0.8	13.3 \pm 0.7
18:2(n-6)	12.2 \pm 1.6	12.7 \pm 1.6	12.4 \pm 1.4	11.8 \pm 1.3*
20:4(n-6)	10.7 \pm 1.3	11.3 \pm 1.0	10.6 \pm 1.1	10.2 \pm 0.9*
20:5(n-3)	0.3 \pm 0.2	0.3 \pm 0.1	0.3 \pm 0.1	0.7 \pm 0.2*
22:6(n-3)	4.4 \pm 0.9	4.9 \pm 1.2	4.4 \pm 1.1	7.8 \pm 1.1*
EPA / AA	0.030 \pm 0.018	0.029 \pm 0.013	0.029 \pm 0.014	0.069 \pm 0.023*
n-6 / n-3	5.2 \pm 1.1	4.9 \pm 1.1	5.3 \pm 1.9	2.8 \pm 0.6*

Values are means \pm SD; Inter-group changes with baseline as covariate: * $p<0.0001$

Table 3. Psychological measures (Hostility-Aggression Questionnaire for Children and Barratt Impulsiveness Scale, version 11)

	Control (n=96)		DHA (n=93)	
	Start	End	Start	End
HAQ-C				
Verbal Aggression	14.0 \pm 2.9	14.7 \pm 3.6	14.7 \pm 3.4	14.6 \pm 3.5
Physical Aggression	24.4 \pm 6.0	25.1 \pm 6.7	24.2 \pm 6.8	25.1 \pm 7.0
Anger	19.7 \pm 4.0	21.2 \pm 5.1	19.2 \pm 4.8	20.0 \pm 5.1
Hostility	23.0 \pm 4.8	23.4 \pm 5.0	22.5 \pm 4.9	23.1 \pm 5.9
BIS-11		(n=83)		(n=85)
Impulsivity	49.7 \pm 9.7	50.4 \pm 10.0	46.3 \pm 9.9	46.1 \pm 10.0

Values are means \pm SD.

the DHA group were significantly reduced to 0.30 in boys ($n=116$, $p=0.003$) and was non-significantly to 0.56 in girls ($n=117$, $p=0.2$) compared with the control group. When both sexes were combined, the odd ratio in the DHA group was reduced to 0.42 compared with controls ($n=233$, $p=0.003$). The odds ratio and p-value altered after adjustment for sex [0.40 (95%CI: 0.23-0.71) and 0.002, respectively]. If both the control and DHA groups were combined, the changes over time in impulsivity were significantly decreased in those without absence during the study period (-0.9 ± 10.1 , $n=116$) compared with those with absence (2.8 ± 9.8 , $n=52$) ($p=0.03$). (The total number of available BIS-11 datasets was 168; see Table 3.) No other parameters of behavior significantly changed between those with and without absence.

Thirty-eight subjects (18 and 20 in the DHA and control groups, respectively) were infected with malaria at the start of the study (smear-positive). Of the smear-negative subjects at the start, eight and four subjects became smear-positive at the end of the study in the control and DHA groups, respectively ($p=0.2$). There were no clinically apparent malaria cases during the study period. Consequently, it was not possible to compare sick days from malaria between groups.

DISCUSSION

As shown in the Introduction, in our previous double-blind study with Japanese school children of similar ages, we found favorable effects of DHA-rich food (3600mg DHA and 840mg EPA per week) on physical aggression.⁶ We could not detect any differences in physical aggression in the present study although the administered amount of DHA and EPA in the present study was similar to the previous one. In the present study, the average scores of physical aggression (about 24, Table 3) were markedly higher than in the case of our previous study in Japan⁶ (estimated to be about 18 after adjustment for the differences in scaling methods). Of course, there might be some differences in sensitivity to detect physical aggression between Japanese and Indonesian versions of HAQ-C, but physical aggression might be too high in subjects in the present study to be controlled with nutrition. A highly significant inverse correlation was found in our previous study between Δ scores of physical aggression and Δ EPA/AA ratios.⁶ The average baseline EPA/AA ratios in the present study were 0.029 to 0.030 (Table 2). These average ratios increased only to 0.07 even after DHA capsule administration, which made a strong contrast with our previous study (baseline average=0.074 to 0.086).⁶ The tissue ratios in Indonesian subjects might be too low even after the intervention to affect physical aggression. These differences might explain why we could not find any significant difference in behavior between groups. Impulsivity was measured by different methods in the two studies. Consequently, it might be difficult to directly compare the results of impulsivity in the two studies.

The most interesting finding was that the inability to perfectly attend school in the DHA group was significantly lower than in the control group, although this parameter was neither primary nor secondary endpoint. Because the present study was a randomized trial per-

formed in a double blind fashion, there was theoretically very little possibility that the results might be distorted with any confounding factors. Moreover, detection of absent children was the easiest parameter in the present study that was determined without question. It is also unlikely that the difference in the attendance rates was found purely by chance, taking the followings into consideration: first, the p-value (0.002 after adjustment for sex) was rather small. We performed about 15 statistical analyses. Bonferroni adjustment of the p-value ($p = 0.002 \times 15 = 0.03$) still demonstrated a significant effect of DHA on the attendance rates. Second, although published only in the form of an abstract,⁷ we found a similar effect of DHA-rich food in a placebo-controlled double-blind trial in Thai children of 8-12 years of age. The number of days absent from school was less than one third in a group of 33 school children who took DHA-rich food for 6 months compared with a control group of 31 children ($p<0.04$).⁷ Besides, published only in the form of an abstract again, providing fish flour-enriched spread significantly lessened the number of days absent from school in a randomized placebo-controlled trial with 355 children for 6 months in South Africa.¹⁵

In the present study we could not elucidate why the absence rates decreased in the DHA group. Those subjects without absence indicated decreased impulsivity compared with those with absence. However, impulsivity did not significantly change by intervention, which suggested that the effects of DHA on school attendance were not explained by their change in impulsivity.

Malaria symptoms might be less severe for subjects who took enough fish oil because of the anti-inflammatory effects of fish oil.¹⁶ Judging from our previous animal study,⁹ it was possible that the duration of malaria symptoms might be shortened. We, therefore, thought that the number of sick days from malaria was smaller in the DHA group than in the control group. Unfortunately, we could not find any clinical cases of malaria in the present study, although about 50 cases of malaria infection were actually found at the start and end of the study by blood smear. The subjects of the present study had all survived about 10 years of life in the malaria-endemic areas. It is likely that they were more or less protected from malaria by preexisting immunity. This was probably the reason why they did not show any apparent malaria symptoms. It was rather difficult to power-calculate a necessary number of subjects to detect a significant result with clinical malaria because no precedent studies of prevention of clinical malaria with fish oil have, to our knowledge, been conducted. In the present study, the extension of the study period to 6 months and blood-smear tests at a two-month interval might have been necessary to obtain a positive result.

In conclusion, fish oil may improve the school attendance rates of children in Lampung, Indonesia. Further investigation is warranted.

ACKNOWLEDGMENTS

We appreciate Dr Miho Itomura, Dr Yoshihiro Terashima, Ms Hiroko Hamatani and Ms Shizuko Takebe for their technical assistance. This study was partly supported by Polyene Project Ltd. and Kentech Co. Ltd..

AUTHOR DISCLOSURES

Kei Hamazaki, Din Syafruddin, Insan S Tunru, Marina F Azwir, Puji BS Asih, Shigeki Sawazaki and Tomohito Hamazaki, no conflicts of interest.

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富含二十二碳六烯酸魚油對行為、學校出席率及瘧疾感染的效應：印尼 Lampung 雙盲隨機安慰劑控制試驗

背景：對一般的學童，只有非常少數的介入性實驗報告說明魚油對學童行為的影響。目的：觀察魚油對於學童的行為及學校出席率的影響。設計：研究對象來自於印尼楠榜省（Lampung Province）的一間小學四到六年級學童（大部分年齡在 9-12 歲），以雙盲的方式將研究對象隨機分派到 DHA 組

（n=116）或控制組（n=117）。在 DHA 組中的研究對象，每天服用 6 顆魚油膠囊（每日 0.65 g DHA 和 0.10 g EPA），持續三個月。控制組則是給予大豆油膠囊。在實驗開始及結束時有抽血及填答兩份問卷：HAQ-C 以及 BIS-11，分別用來評量學童的敵意性-攻擊性及衝動行為。在實驗期間，也記錄學童的到校出席情形。結果：紅血球磷脂質中的 DHA 及 EPA 濃度，在 DHA 組中有顯著的增加。使用 HAQ-C 以及 BIS-11 所檢測的行為，在兩組中並沒有任何差異。然而，與控制組比較，DHA 組學童，實驗期間無法定期上學的可能比率(OR)為 0.40 (95%CI: 0.23-0.71, $p=0.002$)。結論：富含 DHA 的魚油或許可改善印尼楠榜省學童的學校出席率。

關鍵字：行為、紅血球脂肪酸組成、魚油、介入研究、瘧疾、學校出席率