Original Article

Mental retardation is associated with plasma omega-3 fatty acid levels and the omega-3/omega-6 ratio in children

Yasmin H Neggers DrPH[1], Eun-Kyung Kim PhD[2], Ju-Mi Song MA[2], Eun-Jung Chung PhD[3], Young-Sook Um PhD[4], Taesun Park PhD[5]

[1]*Department of Human Nutrition, University of Alabama, Tuscaloosa, Alabama, USA*
[2]*Department of Food Science, Kangnung-Wonju National University, Gangwon-do, Korea*
[3]*Division of General Studies, Kangnam University, Gyeonggi--do, Korea*
[4]*Research Institutes of Food and Nutritional Science, Yonsei l University Seoul,, Korea*
[5]*Department of Food and Nutrition,Brain Korea 21 Project, Yonsei University, Seoul, Korea*

There is evidence that alteration in plasma fatty acid composition may play a role in certain neurological disorders. This case control study was conducted to evaluate the association between plasma fatty acid levels and mental retardation in Korean children. Plasma phospholipid fatty acids, plasma lipids, dietary fatty acids and selected nutrients were measured in 31 mentally retarded boys (mean age 9.93 ±1.5 yrs) and matched controls. Total plasma omega-3 fatty acids (Σω3), docosahexaenoic acid (DHA) and high density lipoprotein (HDL) concentrations were significantly lower and the Σomega-6/Σomega-3 ratio was significantly higher in cases than in controls. The odds in favor of mental retardation increased by 69 % for each unit increase in the Σomega-6/ Σomega-3 ratio (adjusted odds ratio = 1.69, 95% CI = 1.25-2.29). Significant variation in plasma Σomega-3 and the Σomega-6/ Σomega-3 ratio was explained by mental retardation and plasma HDL concentrations (45% and 37 % respectively). There was a significant inverse association between plasma DHA and mental retardation. For each unit increase in plasma DHA, odds of mental retardation decreased by 74 %. There was no significant difference in either total dietary fat or fatty acids intakes between cases and controls. The energy intake of cases was significantly higher than the controls. These results suggest that proportion of plasma Σomega-3 fatty acids, particularly, DHA, and the Σomega-6/ Σomega-3 ratio are associated with mental retardation in children in this study.

Key Words: plasma omega-6 fatty acids, omega-3 fatty acids, docosahexanoic acid, mental retardation, children

INTRODUCTION

During the last two decades, a growing body of research has indicated the involvement, of polyunsaturated fatty acids (PUFA) in the regulation of biochemical events related to neurotransmitter release and uptake in the central nervous system.[1-5] Additionally, there is evidence that omega-3 fatty acids are neuroprotective, and both omega-3 (ω 3) and omega-6 (ω 6) fatty acids have an important function in neurite growth.[4,6] Omega-3 fatty acids are specifically involved in maintaining central system function. Docosahexaenoic acid (C22:6 ω3, DHA) is the predominant omega-3 fatty acid found in the brain and is linked to many aspects of neural function, including neurotransmission, ion channel regulation and gene expression.[7] Mammalian systems do not possess the enzymatic system to synthesize certain polyunsaturated fatty acids such as α-linoleic acid (C18:2 ω 6) and α-linolenic acid (C18:3 ω 3). These fatty acids are converted to a variety of longer and more highly polyunsaturated products that maintain cell membrane integrity.[2] Several investigators have reported significantly reduced levels of linoleic acid, omega-3 fatty acids, particularly DHA, or increased levels of arachidonic acid (ARA) in plasma and red blood cell membranes from different populations suffering from various neurological disorders such as dyslexia, hyperactivity, depression and schizophrenia.[8-14] An impairment of PUFA metabolism has also been hypothesized to occur in children suffering from autistic spectrum disorders. Richardson et al.[11] have reported that a group of children with attention-deficit hyperactivity disorder (ADHD) had many symptoms indicative of essential fatty acid deficiency and had significantly lower percentage of plasma ARA and DHA than did ADHD subjects with few such symptoms and controls. Also, several clinical trials have reported beneficial effects of omega-3 fatty acid supplementation on neural and developmental outcomes in infancy and in treatment of developmental coordination

Corresponding Author: Prof. Yasmin Neggers, Department of Human Nutrition, University of Alabama, Box 870158, Tuscaloosa, AL 35487, USA
Tel: 205-348-4706; Fax: 205-348-2982
Email: yneggers@ches.ua.edu
Manuscript received 4 February 2009. Initial review completed 23 February 2009. Revision accepted 12 March 2009.

disorder in children.[9] Thus, a significant body of research points to associations of PUFA and particularly, omega-3 and omega-6 fatty acid metabolism and possible imbalance in fatty acid composition with various neurological disorders. Mental retardation affects ~ 1% of all school age children, yet the proportion of cases that can be attributed to a known cause is estimated to be only 30 to 50%. Genetic conditions contribute the largest proportion of known causes of mental retardation and Down syndrome is the most frequent cause of mental retardation.[15] Perinatal factors such as infections during pregnancy and perinatal hypoxia and postnatal factors such as brain trauma also account for a significant percentage of cases of mental retardation. However, the etiology of mental retardation, particularly mild mental retardation, has not been delineated for a large proportion of cases. According to some estimates, up to 60% of cases are attributed to unknown etiology.[16] Children with mental disorder have some symptoms similar to those of autism spectrum and other developmental disorders. Given the emerging research which provides a strong biological foundation for the association between various neurological symptoms and PUFAs, understanding the potential effect of abnormalities in plasma fatty acid composition in children with developmental disabilities would have clinical and public health significance. This study was conducted to compare the plasma fatty acid composition in children with mental retardation with matched healthy controls and to examine the association between plasma fatty acid levels and mental retardation.

MATERIALS AND METHODS

Participants and Study Design

Cases for this study consisted of 31 disabled male children (mentally retarded) recruited from a special education school for mentally disabled children located in Seoul (Eunpyung-gu district) in South Korea. Since the prevalence of mental retardation is higher in boys and there were fewer girls enrolled in the special education school, this study was restricted to boys. All the male children diagnosed with mental retardation attending this special education school were invited to participate in this study. Boys older than 13 years were excluded. Forty six eligible cases were identified. Of the eligible cases, 31 boys agreed to enroll in this study. The diagnosis of mental retardation was based on the American Psychiatric Association Diagnostic and Statistical Manuals (DSM) III-R and DSM-IV criteria.[17] Thirty nine percent (n=12) of cases were diagnosed with Down syndrome and the rest of the cases had mental retardation due to unknown causes.

Healthy male children were recruited as controls from an elementary school from the same areas as the special education school from which the cases were selected. The elementary school used for recruiting controls was recommended by the staff of local education boards as having children with similar socioeconomic backgrounds to those of the children attending the special education school. Children with any diagnosed disease were excluded from the control group. To match the average age of cases, grades 2, 3 and 4 were selected from the elementary school for participation in this study. Sixty nine healthy boys were identified as eligible controls for this study. Of the eligible cases and controls, 31 pairs were matched for age and BMI range and participated in this study. Written informed consent was obtained from the parents of both cases and controls. This study was approved by the Institutional Review Board of Kangnung National University. The study period was from Dec. 2002 to March 2003

Biochemical Measurements

A blood sample was obtained from each child after a 12 hour overnight fast. Total lipids of plasma samples were extracted with chloroform-methanol mixture (2:1, v/v) as described by Folch et al.[18] Fatty acid composition of the plasma phospholipids was determined by gas-liquid chromatography (Hewlett-Packard 5890A, USA) with a bonded fused-silica capillary column (Omegawax 320, Supelco, USA; 30m×0.32mm inner diameter). Each peak of fatty acid methyl ester was identified by comparing it with the peak of a standard fatty acid methyl ester (Nu-chek- Prep Inc, USA) and quantified on the basis of the recovery of heptadecanoic acid (Nu-chek-Prep Inc, USA), as an internal standard. The polar (PL) lipids were separated from the extracted lipids by thin layer chromatography on silica gel G-60 (Merck, Darmstadt, Germany). The PL portion was scraped off immediately after the thin-layer chromatography procedure and methylated using the method of Lepage and Roy.[19] Serum lipids and lipoprotein concentrations, including total cholesterol (T-chol), high and density lipoprotein (HDL) were measured in the Eone Reference Laboratory (http://www.eonelab.co.kr). Low density lipoprotein (LDL) concentration was calculated as [LDL = total cholesterol – (TG/5 +HDL-C)].).[20]

Dietary Intakes

One day food intake, representing a typical day, was recorded for both cases and controls. All elementary school children, including those in the special education school, are provided lunch and a mid-morning snack with the same menu. On a selected day, classroom teachers for both cases and controls assisted and recorded dietary intakes. On the same day, parents of all subjects recorded the intake of all the foods consumed at home. Detailed instructions on keeping food records, including portion size information, was provided by a research assistant to both the teachers and parents of all subjects. Information about intakes of foods that contain oil, butter and margarine was recorded in detail, referring to the food labels and other information. Data for fatty acids, total fat, cholesterol as well as other energy and nutrient intakes were calculated using the Computer Aided Nutritional Analysis Program (CAN-Pro, version 2.0) developed by the Korean Society of Nutrition.[21] The Data base for fatty acid composition of common Korean foods contain values for only 480 foods. Therefore, information on total fatty acid intakes for the participants in this study was not complete. However, there was no significant difference in the number of foods for which fatty acid composition was not available between cases and controls. The information on total intakes of energy, energy nutrients, and cholesterol was complete for all participants.

Statistical Analyses

Student's t tests were used to compare the plasma fatty acid levels, plasma lipids, dietary fatty acids and selected nutrient intakes of cases and controls. Logistic regression analyses were used to measure the association between mental retardation (dependent variable) and plasma fatty acid levels. Adjusted odds ratios (AOR) with 95% confidence intervals (C.I.) were calculated to measure the relationship between mental retardation and individual plasma fatty acids, total saturated, mono and polyunsaturated fatty acids as well as Σomega-6, Σomega-3 levels and the Σomega-3/Σomega-6 ratio. The relationship between potential covariates and mental retardation was also assessed using logistic regression; those variables demonstrating significant association were entered as covariates in adjusted models. Covariates used in all logistic regression analyses were: energy intake and HDL concentration.

Linear multiple regression analyses were used to evaluate the relationship between mental retardation (independent variable) and various plasma and dietary fatty acids **(**Σomega-6, Σomega-3 levels and the Σomega-6/Σomega-3 ratio) as dependent variables. Initially both HDL and energy intake were used as a covariate in these multiple regression models. The regression coefficient for energy intake was not significant in any of these models and therefore was removed from these models. SAS version 9.3 was used to conduct statistical analyses.

RESULTS

Subjects for this study consisted of 31 pairs of cases and healthy controls matched for age and BMI range. There was no significant difference in mean age (9.93 ±1.5 vs. 9.90 ± 1.4 yrs, $p = 1.0$) or BMI (18.5 ± 4.1 vs. 17.9 ± 2.5, $p = 0.45$) between cases and controls. The average household income, years of education and mother's age at childbirth was not significantly different in cases and control children ($p > 0.05$)

Plasma phospholipid fatty acid composition:

Plasma phospholipid fatty acid (PFA) composition of cases and controls is presented in Table 1. The proportions of total plasma mono- and polyunsaturated fatty acids were significantly higher and the proportion of total saturated fatty acids was significantly lower in cases than in controls. Total omega-3 fatty acids particularly, DHA levels were significantly lower in cases as compared to controls. On the other hand, levels of total omega-6 fatty acids were significantly higher in cases resulting in a higher Σomega-6/Σomega-3 ratio in cases than in controls ($p < 0.0001$). There was no significant difference in EPA or ARA levels between the two groups ($p = 0.68$ and 0.18 respectively).

Dietary fatty acid composition and selected nutrients:

A comparison of dietary fatty acid composition of cases and controls is presented in Table 2. There was no significant difference in total saturated, monounsaturated, polyunsaturated, omega-3, and omega-6 fatty acid intakes between the two groups. As indicated in the methods section, fatty acid content of some foods was not available in the software package used to calculate the nutrient intake of the subjects. Therefore, the total mean fatty acid (saturated, monounsaturated and polyunsaturated) intakes of both cases and controls were lower than the total mean fat intakes of cases and controls. The total mean fatty acid intakes as calculated from foods for which fatty acid composition was available were 32.6 ± 11.4 g for cases and 30.10 ± 17.2 g for control ($p = 0.46$), while the total fat intakes for all the foods consumed by cases and controls were 47.00 ± 17.4 and 55.2 ± 19.0 g ($p = 0.09$) respectively (Table 3). There was no significant difference between the total dietary cholesterol or protein intakes between cases and controls (Table 3). However, the mean carbohydrate (243.2 ± 2.0 vs. 287.7 ± 78.1 g, $p = 0.01$) and hence the total energy intake of cases was significantly lower than that of controls (1,648 ± 405.2 vs.1, 930 ± 485.3 kcal, $p = 0.018$).

Associations between plasma lipids/lipoproteins, dietary lipids and mental retardation:

There was no significant association between any of the plasma lipid fractions (total cholesterol, LDL and HDL) and energy, dietary fat, type of fat as well as total choles-

Table 1. Plasma phospholipid fatty acid composition of cases and controls

Fatty Acid (FA) Concentration (g/100 g total fatty acids)	Group		
	Cases n=31	Controls n=31	*p*
Saturated FA			
C14 : 0	1.67±0.39	1.83±0.27	0.05
C16 : 0	28.63±2.44	26.52±1.74	0.0002
C18 : 0	18.25±1.85	22.37±1.64	<0.0001
C20 : 0	0.28±0.26	0.21±0.13	0.25
C22 : 0	0.03±0.01	0.05±0.02	0.0003
C24 : 0	0.11±0.10	0.29±0.14	<0.0001
Total Saturated FA	48.98±1.92	51.28±2.46	0.0001
Monounsaturated FA			
C16 : 1	0.64±0.37	1.33±0.20	<0.0001
C18 : 1	17.79±3.08	16.62±1.05	0.05
C20 : 1	0.26±0.12	0.42±0.12	<0.0001
C24 : 1	2.10±1.71	0.52±0.21	<0.0001
Total Monounsaturated FA	20.80±3.63	18.89±1.13	0.006
Polyunsaturated FA			
C18 : 2ω 6	9.46±3.15	5.21±2.16	<0.0001
C20 : 3 ω 6	1.37±0.48	1.17±0.83	0.28
C20 : 4 ω 6 (ARA)	7.86±1.75	8.02±1.18	0.68
C22 : 4 ω 6	0.06±0.08	0.30±0.10	<0.0001
C22 : 5 ω 6	0.21±0.23	0.39±0.08	<0.0001
Total omega-6 FA (Σω 6)	18.96±3.19	15.09.±2.65	<0.001
C18 : 3 ω3	0.27±0.13	0.30±0.11	0.46
C20 : 5 ω 3 (EPA)	0.47±0.28	0.42±0.22	0.18
C22 : 5 ω3	0.14±0.13	0.01±0.01	<0.0001
C22 : 6 ω 3 (DHA)	2.93±1.71	5.14±1.03	<0.0001
Total omega-3 FA (Σω 3)	3.80±1.66	5.87±1.15	<0.0001
Total Polyunsaturated FA	22.77±3.39	20.96±2.70	0.02
Σω 6/ Σω 3	6.03±2.76	2.75±1.21	<0.0001
*Other fatty acids	7.44±1.62	8.88±2.68	0.101
Total	100.00	100.00	

*These fatty acids could not be identified and were not included in analyses.

Table 2. Fatty acid intakes of cases and controls

Fatty Acid Intakes (g)	Cases Mean ± SD	Controls Mean ± SD	*p*
Saturates Fatty Acids			
C4:0	0.08±0.07	0.08±0.05	0.60
C6:0	0.01±0.06	0.08±0.05	0.43
C8:0	0.07±0.05	0.06±0.04	0.43
C10:0	0.20±0.13	0.17±0.10	0.44
C12:0	0.30±0.19	0.26±0.16	0.46
C14 : 0	1.19±0.65	1.15±0.69	0.55
C16 : 0	7.47±2.8	6.73±4.7	0.95
C18 : 0	3.02±1.3	3.21±1.9	0.60
C20 : 0	0.07±0.03	0.07±0.04	0.85
C22 : 0	0.04±0.02	0.03±0.02	0.50
Total saturated fatty acids	13.43±5.80	12.99±7.60	0.51
Monounsaturated Fatty Acids			
C10:1	0.01±0.00	0.01±0.01	0.77
C16 : 1	0.61±0.41	0.77±0.52	0.19
C18 : 1	10.11±4.3	11.15±7.14	0.49
C20 : 1	0.14±0.20	0.13± 0.14	0.91
C22 : 1	0.04±0.24	0.03±0.15	0.87
C24 : 1	0.02±0.02	0.04±0.12	0.19
Total monounsaturated fatty acids	12.33±4.35	10.52±7.25	0.12
Polyunsaturated Fatty Acids			
C18 : 2 ω 6	5.51±2.54	5.49±3.63	0.99
C 20:2 ω 6	0.07±0.05	0.09±0.08	0.36
C20 : 3 ω 6	0.10±0.06	0.10±0.08	0.65
C20 : 4 ω 6	0.01±0.01	0.02±0.02	0.95
Total ω 6	5.70±2.56	5.69±3.71	0.96
C18 : ω 3	0.52±0.32	0.47±0.32	0.61
C18 : 4 ω 3	0.01±0.04	0.01±0.03	0.76
C20 : 5 ω 3	0.05±0.13	0.03±0.08	0.40
C22 : 5 ω 3	0.01±0.01	0.01±0.01	0.68
C22 : 6ω 3	0.09±0.28	0.04±0.17	0.46
Total ω3	0.67±0.56	0.55±0.50	0.40
Total polyunsaturated fatty acids	6.83±3.41	6.57±3.76	0.76

terol intakes in either cases or controls. Similarly, there was no association between plasma phospholipid Σomega-3, Σomega-6, the Σomega-6/Σomega-3 ratio and energy as well as total dietary fat, dietary Σomega-3 and Σomega-6 fatty acids intakes in either cases or controls.

The mean total plasma cholesterol (3.91 ± 0.52 vs. 4.48 ± 0.65 mmol/L, $p = 0.0004$), LDL (2.27 ± 0.40 vs. 2.53 ± 0.60 mmol/L, $p = 0.045$) and HDL (1.21 ± 0.23 vs. 1.53 ± 0.29 mmol/L, $p < 0.0001$) levels of cases was significantly lower than that of controls. Only in cases was there a significant positive association between plasma HDL and both DHA (r = 0.55, $p = 0.003$) and Σomega-3 (r = 0.49, $p = 0.005$) and an inverse association between plasma HDL levels and the Σomega-6/Σomega-3 ratio (r = -0.38, $p = 0.04$). Mental retardation was significantly associated with plasma HDL concentration [odds ratio (OR) = 0.88, 95 % CI = 0.88 - 0.94]. Total plasma cholesterol and LDL levels were not associated with mental retardation.

Table 3. Dietary intakes of selected nutrients in cases and controls

Dietary Intakes	Cases n=31	Controls n=31	*p*
Energy (kcal)	1,648.0±405.2	1,930.0±485.3	0.018
Plant fat (g)	20.6±8.5	27.4±12.7	0.02
Animal fat (g)	26.4±13.6	27.8±13.3	0.068
Total fat (g)	47.0±17.4	55.2±19.0	0.09
Protein (g)	63.5±17.1	72.3±19.7	0.073
Carbohydrate (g)	243.2±19.0	287.7±78.0	0.015
Cholesterol (mg)	260.0±143.5	281.2±194.0	0.63

Association between plasma phospholipid fatty acids and mental retardation:

Logistic regression analyses were utilized to measure the association between mental retardation and plasma fatty acids. Energy intake was adjusted in all the models due to the difference in energy intake between cases and controls. Also, since plasma HDL was associated with both mental retardation and plasma Σomega-3 and Σomega-6/Σomega-3, it was used as a covariate in all the regression analyses. Total plasma saturated fatty acid level was significantly associated with mental retardation (adjusted odds ratio or AOR = 0.63, 95 % CI = 0.47-0.85) (Table 4). There was no significant association between mental retardation and either total plasma mono- or polyunsaturated fatty acid levels. However, plasma Σomega-3, Σomega-6 and the Σomega-6/Σomega-3 were significantly associated mental retardation. The odds in favor of mental retardation increased significantly with an increase in Σomega-6 level (AOR=1.26, 95% CI = 1.10-1.53). Conversely, there was a significant reduction in odds of mental retardation with an increase in plasma Σomega-3 level. There was 58 % reduction in odds of mental retardation for each unit increase in Σomega-3 level (AOR =0.42, 95% CI = 0.27-0.66). Consequently, the odds of mental retardation were estimated to increase by 69 % for each unit increase in the Σomega-6/Σomega-3 (AOR =1.69, 95 % CI = 1.25-2.29). Plasma DHA level was also significantly associated with mental retardation. For each unit increase in plasma DHA, odds of mental retardation decreased by 49 % (AOR = 0.51, 95% CI = 0.29-0.87). There was no association between EPA or ARA level and mental retardation. After adjusting for Σomega-6/Σomega-3, total plasma saturated fatty acids was not significantly associated with mental retardation.

In multiple regression analyses, mental retardation as an independent variable was significantly associated with Σomega-3 ($\beta = 1.3$, $p = 0.002$, $R^2 = 45\%$), Σomega-6 ($\beta = -4.3$, $p < 0.0001$, $R^2 = 31$ %) and the Σomega-6/Σomega-3 ($\beta = -2.7$, $p < 0.0001$, $R^2 = 40\%$) after adjusting for plasma HDL concentration. A significant 45, 40 and 31% of variation in plasma Σomega-3, Σomega-6/Σomega-3, and Σomega-6 respectively, was explained by independent variables: mental retardation and plasma HDL concentration. Also, there was a significant association between plasma DHA and mental retardation ($\beta = 1.4$, $p = 0.0006$, $R^2 = 0.50$). Plasma DHA level was 1.4 g higher in controls than in cases after adjusting for HDL concentrations.

Table 4. Association* between plasma fatty acid levels and mental retardation

Plasma Fatty Acid Concentrations (g/100 g total fatty acids)	Group				
	Cases n=31	Controls n=31	*Adjusted Odds Ratio (AOR)	95 % Confidence Interval	*p*
Total saturated fatty acids	48.98±1.92	51.28±2.46	0.63	0.47-0.85	0.003
Total monounsaturated fatty acids	20.80±3.63	18.89±1.13	1.33	1.06-1.65	0.061
Total poly-unsaturated fatty acids	22.77±3.39	20.96±2.70	1.19	0.99-1.00	0.062
Total ω 6 fatty acids	18.96±3.19	15.09±2.65	1.26	1.10-1.53	0.017
Total ω 3 fatty acids	3.80±1.66	5.87±1.15	0.42	0.27-0.66	0.0001
ω 6/ω 3 ratio	6.03±2.76	2.75±1.21	1.69	1.25-2.29	0.0007

*Separate logistic regression models were fitted for each type of fatty acids and all models were adjusted for total energy intake and plasma HDL levels.

There was no association between mental retardation and ARA or EPA.

DISCUSSION

Alteration in plasma and red blood cell fatty acid composition, particularly omega 3 and omega 6 fatty acids levels in children suffering from various neurological disorders such as dyslexia, attention deficit hyperactivity, depression and schizophrenia has been reported.[11-13] However, the relationship between plasma fatty composition and mental retardation has not been evaluated. Though a significant proportion of cases with mental retardation are of unknown etiology, studies have indicated that risk is higher among males, low birth weight children, multiple births, and children born to women older at age of delivery, and lower level of education.[15] In this study there were no significant differences in age at delivery and level of maternal education between cases and controls. Birth weights of children were not available but all the children were singletons. In the present study, a significant association between mental retardation and Σomega-3, Σomega-6 and the Σomega-6/Σomega-3 ratio was observed. The plasma Σomega-6 level was significantly higher and Σomega-3 fatty acids level was significantly lower in children with mental retardation as compared to that of healthy controls (Table 1). The plasma fatty acid composition in healthy controls in our study was similar to that reported for children by other investigators. We could locate only one study, conducted by Vancassel et al. [10] which evaluated the plasma fatty acid levels in children with mental retardation. The total saturated, monounsaturated and Σomega-6 fatty acid levels of children with mental retardation in this study were similar to our study. However, the Σomega-3 levels were lower (2.5 ± 0.8 g/100 g total fatty acids) and hence the Σomega-6/ Σomega-3 ratio (11.0 ± 3.1) in children with mental retardation was higher than that of cases in our study (6.03 ± 2.76). Vancassel et al.[10] did not evaluate the association between plasma fatty acid levels and mental retardation. Similar to our results, Burgess et al.[12] have reported lower proportions of plasma DHA in children with severe symptoms of hyperactivity as compared to controls. They also indicated that subjects with a low level of Σomega-3 had significantly more behavioral problems than did those with high proportions of omega-3 fatty acids. Also, in a recent study, Colter et al.[22] reported that adolescents with ADHD display abnormal fatty acid profiles and have significantly lower red blood cell DHA and omega 3 fatty acid levels than control subjects.

An interesting observation in the current study was that plasma HDL concentration was associated with mental retardation, DHA and Σomega-3 levels. Cases had significantly lower HDL, Σomega-3 and DHA levels than controls. The differences in phospholipids contained in various plasma lipoproteins are small but HDL phospholipids constitute the major part of plasma phospholipids.[23] It is therefore possible that lower HDL levels in cases in our study may result in lower total omega-3 fatty acids and DHA levels in cases as compared to controls. However, even after adjusting for HDL concentrations the proportion of both Σomega-3 (Table 4) and DHA were significantly lower in cases than controls. Since the fatty acid composition of phospholipids partially reflects that of the diet,[24] it is possible that a more precise long term measurement of intake of total fat, omega-3 and omega-6 fatty acids as measured by validated food frequency questionnaire may explain the differences in fatty acid composition between cases and controls. Another significant factor associated with plasma HDL concentration, physical activity, was not evaluated in this study. However, there was no significant difference in the BMI of cases and controls.

The finding of a lower proportion of plasma DHA in children with mental retardation in this study is of significance because DHA is a predominant fatty acid found in the brain and has been linked with many aspects neural functions, including neurotransmission, membrane fluidity, enzyme regulation and gene expression.[25] Plasma is a primary source of DHA for tissues and more than 95% of the DHA in the plasma is present in plasma lipoproteins.[26,27] Thus it is possible that lower plasma levels of omega -3 fatty acids and DHA in cases in this study may be an indication of lower availability of these fatty acids to the brain

The mechanism of alteration in plasma fatty acid composition in children with mental retardation is not clear. . It is plausible that the associations observed in our study are confounded due to the differences in rate of absorption, bio-availability and composition of dietary fats in cases and healthy control. Another possible reason for a lower Σomega-3 fatty acid level in mentally retarded children might involve enhanced catabolism of omega-3 fatty acids in plasma phospholipids. In schizophrenic patients, the activity of enzyme phospholipase A2 has been

reported to increase in plasma and platelet membranes, which subsequently accelerates the breakdown of PUFA and a decreased PUFA content is inserted in membranous phospholipids.[28] It is also plausible that lower DHA and other omega-3 fatty acids synthesis may be a result of impaired conversion of the fatty acid precursors to their longer more highly unsaturated omega-3 products. Possible sites for this inefficiency include desaturases steps.[29]

A limitation of our study is that food intake was recorded for only one day. Food frequency questionnaires which measure the long term intake would have provided a better estimate of past dietary intakes. A more precise measure of dietary intake may detect an association between dietary and plasma fatty acids which might not have been apparent by measuring fatty acid intakes with a one day food intake record. Another limitation of this study is that since this study was restricted to male children, the results of this study cannot be generalized to females and older adults.

To our knowledge, this is the first matched cases control study conducted in South Korean children which evaluated the association between mental retardation and both the plasma and dietary fatty acid composition. The results of this study have clinical implications. Because Σomega-3 fatty acids, particularly DHA, are present in large amounts in certain regions of the brain, low concentration of these fatty acids in these regions may affect brain function. Based on our findings we suggest that plasma Σomega-3 fatty acids and DHA may be predictors of mental retardation, especially when no other plausible factors can be identified. Larger studies with better measures of long term dietary intakes, particularly foods rich in omega-3 fatty acids are needed to clarify and confirm the association between plasma omega-3 fatty acids and mental retardation.

ACKNOWLEDGEMENT:
This study was supported by a grant (02-PJ1-PG3-22003-0005) from the Ministry of Health &Welfare, Republic of Korea

AUTHOR DISCLOSURES
There is no financial or other conflict of interest regarding this manuscript.

REFERENCES

1. Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR, Burgess JR. Essential fatty acid metabolism in boys with attention deficit hyperactivity disorder. Am J Clin Nutr. 1995;62:761-8
2. Horrobin DF, Bennett CN. Phospholipid metabolism and the pathophysiology of psychiatric disorders. In: Peet M, Glen AIM, Horrobin GF editors. Phospholipid Spectrum Disorders in Psychiatry and Neurology. Carnforth, UK: Marius press; 2003. p.3-48.
3. Kapoor R, Huang YS. Gamma linolenic acid: an anti-inflammatory omega-6 fatty acid. Curr Pharm Biotechnol. 2006:7:531-4.
4. Lauritzen I, Blondeau N, Heurteaux C, Widmann C, Romey G, Lazdunski M. Polyunsaturated fatty acids are potent neuroprotectors. EMBO J. 2000;19:1784-93.
5. Scaglioni S, Veduci E, Agostoni C, Vergani B, Stival G, Riva E, Giovannini M. Dietary habits and plasma fatty acids levels in a population of Italian children: is there any relationship? Prostaglandins Leukot Essent Fatty Acids. 2004; 71:91-5.
6. Young GS, Conquer JA, Thomas R. Effect of randomized supplementation with high dose olive, flax or fish oil on serum phospholipid fatty acid levels in adults with attention deficit hyperactivity disorder. Reprod Nutr Dev. 2005;45: 549-58.
7. Young G, Conquer J. Omega-3 fatty acids and neuropsychiatric disorders. Reprod Nutr Dev. 2005;45:1-28.
8. Conklin SM, Manuck SB, Yao JK, Flory JD, Hibbeln JR, Muldoon MF. High omega-6 and low omeg-3 fatty acids are associated with depressive symptoms and neuroticism. Psychosom Med. 2007;69(9):932-4.
9. Hoyos C, Almqvist C, Garden F. Xuan W, Oddy W, Marks GB, Webb KL. Effect of omega 3 and omega 6 fatty acid intakes from diet and supplements on plasma fatty acid levels in the first 3 years of life. Asia Pac J Clin Nutr. 2008;17: 552-7.
10. Vancassel S, Durand G, Barthelemy C, Lejeune B, Martineau J ,Guilloteau D, Andres C, Chalon S. Plasma fatty acid levels in autistic children. Prostaglandins Leukot Essent Fatty Acids. 2001;65:1-7.
11. Richardson AJ, Ross MA. Fatty acid metabolism in neurodevelopment disorder; a new perspective on associations between attention deficit/ hyperactivity disorder, dyslexia, dyspraxia and autistic spectrum. Prostaglandins Leukot Essent Fatty Acids. 2000;63:1-9.
12. Burgess JR, Stevens L, Zhang W, Peck L. Long chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. Am J Clin Nutr. 2000;71(Suppl):S327-30.
13. Sliwinski S, Croonenberghs J, Christophe A, Deboutte D, Maes M. Polyunsaturated fatty acids: do they have a role in pathophysiology of autism? Neuro Endocrinol Lett. 2006; 27(4):465-71.
14. Bell JG, Mackinlay EE, Dick JR, MacDonald DJ, Boyle RM, Glen ACA. Essential fatty acids and phospholipase A2 in autistic spectrum disorders. Prostaglandins Leukot Essent Fatty Acids. 2004;71:201-4.
15. Croen LA, Grether JK, Slevin S. The epidemiology of mental retardation of unknown causes. Pediatrics. 2001;107(6): e-86.1410.
16. Murphy CC, Boyle C, Schendel D, Decoufle P, Yeargin-Allsopp M. Epidemiology of mental retardation in children. Mental Retard Dev Disab Rev.1998;4:6-13
17. American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders, 4th edition, DSM IV. Washington, DC: American Psychiatric Press; 1994.
18. Folch J, Less M, Stanley GHS. A simple method for the isolation and purification of total lipids from animal tissues. J Biol Chem. 1957;226:497-509.
19. Lepage G, Roy GC. Direct trans-esterification of all classes of lipids in a one step reaction. J lipid Res. 1986; 7:114-29
20. Fridwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.
21. Korean Society of Nutrition. Computer Aided Nutritional Analysis Program (CAN-Pro, version 2.0) 2005.
22. Colter AL, Cutler C, Meckling KA. Fatty acid status and behavioural symptoms of attention deficit hyperactivity disorder in adolescents: a case control study. Nutr J. 2008;7:8-15.
23. Noori M, Darabi M, Rahimipour A, Rahbani M, Abadi NA, Darabi M, Ghatrehsamani K. Fatty acid composition of

HDL phospholipids and coronary artery disease. J Clin Lipidology. 2009;3:39-44.
24. Hodges AM, Simpson JA, Gibson RA, Sinclair AJ, Makides M, O. Dea K, English DR, Giles GG. Plasma phospholipid fatty acid composition as a biomarker of habitual dietary fat intake in an ethnically diverse cohort. Nutr Metabolism Cardiovascular Dis. 2007;17:415-26.
25. Innis S.M. Dietary (n-3) fatty acids and brain development. J. Nutr. 2007;137:855-9.
26. Polozova A, Gionfriddo E, Salem N. Effect of docosahexaenoic acid on tissue targeting and metabolism of plasma lipoproteins. Prostaglandins Leukot Essent Fatty Acids. 2006;75:183-90.
27. Lefkowitz SY, Lim YH, Salem N. Where does the developing brain obtain its docosahexaenoic acid? Relative contributions of dietary alpha-linolenic acid, docosahexaenoic acid and body stores in the developing rat. Pediatr Res. 2005;57;157-65.
28. Horrobin DF. The membrane phospholipids hypothesis as a biochemical basis for the neurodevelopment concept of schizophrenia. Schizophr Res. 1998;30:193-208
29. Horrobin DF, Bennett CN. New gene targets related schizophrenia and other psychiatric disorders: enzymes, binding proteins and transport proteins involved in phospholipid and fatty acid metabolism. Prostaglandins Leukot Essent Fatty Acids. 1999;60:141-67.

Original Article

Mental retardation is associated with plasma omega-3 fatty acid levels and the omega-3/omega-6 ratio in children

Yasmin H Neggers DrPH[1], Eun-Kyung Kim PhD[2], Ju-Mi Song MA[2], Eun-Jung Chung PhD[3], Young-Sook Um PhD[4], Taesun Park PhD[5]

[1]*Department of Human Nutrition, University of Alabama, Tuscaloosa, Alabama, USA*
[2]*Department of Food Science, Kangnung-Wonju National University, Gangwon-do, Korea*
[3]*Division of General Studies, Kangnam University, Gyeonggi--do, Korea*
[4]*Research Institutes of Food and Nutritional Science, Yonsei l University Seoul,, Korea*
[5]*Department of Food and Nutrition,Brain Korea 21 Project, Yonsei University, Seoul, Korea*

兒童智力遲緩與血漿中 ω-3 脂肪酸及 ω-3/ω-6 比率相關

有研究指出血漿中脂肪酸組成改變對特定的神經異常有關。這個病例對照研究評估韓國小孩血漿中脂肪酸與智力遲緩之相關。測量 31 位智能遲緩之男孩(平均年齡為 9.93±1.5 歲)及其配對控制組之血漿中磷脂脂肪酸、脂質、飲食脂肪酸及營養素。病例組血漿之 ω-3 脂肪酸(Σω3)、二十二碳六烯酸(DHA)及高密度脂肪酸(HDL)濃度顯著低於控制組，而 ω-6/ω-3 比率顯著高於控制組。結果發現 ω-6/ω-3 比率每增加一單位，智能遲緩勝算比增加 69%(校正後勝算比為 1.69，95%信賴區間為 1.25-2.29)。顯著的血漿 Σω3 及 Σω-6/Σω-3 比率之變異，能被智能遲緩及其血漿中高密度脂蛋白濃度解釋(分別為 45%及 37%)。血漿中 DHA 與智能遲緩有顯著之逆相關。血漿中 DHA 每增加一單位，智能遲緩之勝算比可降低 74%。在病例及對照組之飲食脂肪及脂肪酸攝取未達顯著差異。病例組能量之攝取顯著高於控制組。本研究發現，血漿 Σω3 脂肪酸、DHA 及 Σω6/Σω3 比率與孩童智能遲緩相關。

關鍵字：血漿 ω-6 脂肪酸、血漿 ω-3 脂肪酸、二十二碳六烯酸、智力遲緩、孩童