Original Article

Genetic variants of FADS gene cluster, plasma LC-PUFA levels and the association with cognitive function of under-two-year-old *Sasaknese* Indonesian children

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Background/Aims: Long-chain polyunsaturated fatty acids (LC-PUFA) are regarded as essential for child cognition. Genetic variation in fatty acid (FA) desaturase enzyme (FADS) has been recognized as an important effect modifier in the relation between LC-PUFA and child cognitive function. This study aimed to identify the distribution of genetic variant (genotype) SNP rs174468 and to assess plasma FA and developmental outcome by the genotype among under-2 year old Sasaknese Indonesian children. **Methods**: Data was collected at baseline of a randomized trial (NUPICO, clinicaltrials.gov NCT01504633) in East Lombok district, Indonesia. Breastfed, 12-17 month old children were recruited and 240 subjects were included in the study. Child cognition was assessed as Bayley Mental Developmental Index (MDI). **Results**: From 206 subjects whose blood samples can be collected, only two genotypes were found (90.3% GG homozygotes, 9.7% AG heterozygotes), and minor allele AG was significantly associated with higher level of arachidonic acid (20:4 n-6), n-6 LC-PUFA and FADS1 index. MDI score was associated with a FADS2 index (DHA:EPA ratio) but not genotype (Adjusted R-square= 0.043). **Conclusions**: FADS2 index was associated with cognitive function. No difference was found between children with GG and AG genotypes who were all breastfed and not low birth weight.

Key Words: cognitive function, FADS, Indonesia, LC-PUFA, under-two-year-old children

INTRODUCTION

The importance of long chain polyunsaturated fatty acid (LC-PUFA) on developmental outcomes of children is well recognized and more recently, research has focused on the mechanisms underpinning the role of essential nutrients on early life development. Deficiencies of LC-PUFA have significant effects on the developmental phase of the brain especially in the third trimester of pregnancy and the first two years of life where brain growth spurt occurs.[1] Seafood is rich in specific LC-PUFAs and maternal fish consumption has shown benefits on both short term (higher novelty preference on visual recognition memory) and long term (higher scores of verbal intelligence quotient and other Behavioural outcome) development of young children.[2-4] Pregnant mothers are therefore recommended to take PUFAs in particular from those derived from marine sources for sufficient supply of PUFAs to the fetus.[5] However, it is also recognized that not all trials have shown consistent effects of LC-PUFA on developmental outcome of young children and the role of gene-nutrient interactions especially related to FADS polymorphisms has gain interest as an effect

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modifier.

The efficient use of these LC-PUFAs depends on the activity of desaturase enzyme in the metabolic pathway of fatty acid. Linoleic and α-linolenic acid obtained from dietary largely plant-based sources are converted to long chain fatty acids by the enzymes Δ-5 desaturase (D5D) and Δ-6 desaturase (D6D) through the desaturation and elongation pathway where *FADS1* and *FADS2* genes encode these rate limiting enzymes.[6] Studies have shown that individual genetic variations might affect how these omega-3 and omega-6 were metabolized in body.[7-9] Polymorphism of the FADS gene cluster and ELOVL2 gene has been reported to be associated with variation in LC-PUFA plasma levels.[10] Caspi reported that the effect of breast feeding on cognitive function was modulated by genetic variant on FADS gene in which carrier of the major allele of the SNP (rs174575) had a higher IQ compared to carriers of the minor allele.[11] On the other hand, a different finding was reported by Morales in which all the breast fed children have advantage on IQ over non breast-fed children regardless of their genetic variant SNP (rs174468).[12] It was also found that children with the homozygous minor allele for the SNP (rs174468) had the lowest IQ score if they were not breast-fed but once they were breast fed, the highest IQ scores were reported. These findings stimulated us to further investigate the role of SNP rs174468 on the PUFA level and its association to developmental outcomes among Indonesian children.

In Indonesia, the prevalence of the gene polymorphism FADS2 among under-2 year children has not been studied yet. Evidences suggest that it is important to understand the role of these genetic factors on the fatty acid metabolism to achieve the optimal development of all children. It is possible that the needs of fatty acids can be optimized according to the genetic profiles to achieve optimal intelligence. The aim of this study was to identify the distribution of genetic variant (genotype) SNP rs174468 and to assess the plasma fatty acid concentration and developmental outcome by the genotype among under-2 year old Sasak ethnic Indonesian children.

METHODS

The data for this study were collected at baseline of a randomized trial (NUPICO) registered at clinicaltrials.gov as NCT01504633. Ethical approval was obtained from the Faculty of Medicine, University of Indonesia (568/PT02.FK/ETIK/2011). The study was conducted in 2012 in the East Lombok district, West Nusa Tenggara province, Indonesia. Breast-fed, 12-17 month old children of Sasak ethnicity were recruited with the exclusion criteria: low birth weight (<2500 g), congenital disorder, severe anaemia (Hemoglobin <70 g/L) and having malaria infection. A total of 240 subjects were included in the study.

Anthropometric measurements

Anthropometric measurements were done by trained persons following standard method.[13] The recumbent length of child was measured to the nearest 0.1 cm by using a Shorrboard and the weight to the nearest 0.1 kg by using a SECA 770 weighing scale.

Measurement of LC-PUFA

The plasma PUFA concentration was analyzed by using the Gas Chromatography-Fatty Acid Methyl Esther (GC-FAME) method (AOAC, 2005) in the local health laboratory of Jakarta (Laboratorium Kesehatan Daerah, Labkesda DKI). Fatty acid methyl ester were separated and quantified in Agilent Technologies 6890 Gas Chromatograph (Hewlett Packard, USA) with auto sampler and Flame Ionisation Detector and Chemstation data system by using HP Ultra 1 capillary column 50 m x 0.20 mm x 0.11 μm film thickness (J&W Scientific, Folsom, CA, USA). Fatty acid methyl esters were identified based on the retention time to authentic lipid standards (SULPECOTM 37 Component FAME MIX) and quantified by comparison between sample peak areas to internal standard and expressed as μg/mL.

Genotyping procedure

DNA extraction was done using Gene Aid Kit (# GB300, Taiwan, Republic of China). SNP Genotyping analysis was done to identify the Allele type of Rs 174468 polymorphism. The method used was Taqman Assay using 2 allele-specific probes and a pair of primers to specifically distinguish/detect the type of genotype/allele i.e. Applied Biosystem Taq Man SNP Genotyping Assay MTO ID C_2547998_10 (Cat. 4351379, New York, USA) and GTX press master mix (Cat. 4371353, New York, USA) kits. Step One™ Real Time PCR-system with 48-well thermo bloc instrument and StepOneV2.3 software (AB) was used for the analysis of SNP genotyping assay.

Assessment of developmental outcome

For developmental outcome, mental developmental index (MDI) was assessed using Bayley Scales of Infant Development II, BSID-II by trained psychologist.[14]

Statistical analyses

Continuous variables (MDI and PDI scores, levels of plasma fatty acids) were tested for normal distribution using one-sample Kolmogorov-Smirnov test. Differences in those variables between maternal/child genotypes were tested using unpaired T-test for normally distributed data or Mann-Whitney U test for non normally distributed data (for continuous variables) or Chi-square test (for categorical variables).

Linear regression analyses were conducted with each of the fatty acids and ratios (as proxies of FADS indices, $p<0.2$ in bivariate analyses) with SNP of rs 174468 as independent variable. An additive model was applied with homozygous major allele carriers (GG) coded as 0 and heterozygous subjects as 1, with the assumption of a linear relation between fatty acid outcomes and number of minor alleles.

RESULTS

Homozygote GG of the rs 174468 (FADS cluster) was the dominant type amongst the study subjects (90.3%, n=186) while heterozygote AG was found in only 9.7% (n=20) and none of the 206 subjects whose blood samples can be collected had AA homozygote. The GG and AG groups were comparable in gender, age, birth weight and nutritional status. In line with the inclusion criteria of the

intervention study, none of the subjects were born prematurely and all were still breastfed. There was no difference in dietary diversity score and proportion of children consuming fish in the last 24 hours. There was no difference in developmental scores (MDI and PDI) between the GG and AG groups (Table 1).

The AG genotype was significantly associated with higher level of arachidonic acid (20:4 n-6), n-6 LC-PUFA, ETA and FADS1 index (Table 2). The association remained significant after controlling for fish intake for arachidonic acid (20:4 n-6), n-6 LC-PUFA, and FADS1 index (data not shown).

When stratified by genotype, the correlation between log FADS2 indices (DHA:EPA ratios) and MDI scores tended to be significant (r=0.648, p=0.059) in AG genotype but not in GG genotype. There was no significant correlation between MDI and FADS1 (AA:DGLA) or the other FADS2 (DGLA:AA) indices (Table 3). Multiple linear regression predicting MDI score with fatty acid levels, genotype and fish intake showed that MDI score was associated with a FADS2 index (DHA:EPA ratio) but not genotype (Table 4).

DISCUSSION

In this study we explored the impact of SNP rs 174468 genotype of FADS cluster of the local Sasak ethnicity in the island of Lombok. The finding revealed major allele homozygotes (GG) of rs 174468 is the dominant type in the local population. Carriers of the minor allele (AG) were associated with higher FADS1 index and n-6 fatty acid levels (arachidonic acid and n-6 LCPUFA) but there was no difference in cognitive function (MDI score) amongst these breastfed children. We found that cognitive function was positively associated with FADS2 index (DHA:EPA).

In the present study, MDI score of the children was

Table 1. General characteristics, nutritional status and developmental scores of the children by genotype[†]

Variables	GG (n=186)	AG (n=20)	p-value[‡]
General characteristics			
Sex: boy (%)	49.5	50.0	0.575
Age (month)	14.1±1.4	14.1±1.3	0.968
Birthweight (grams)	3,200 (3,000-3,500)	3,300 (2,850-3,500)	0.981
Age of introduction of first complementary food (mo)	6.0 (5.0-6.0)	6.0 (4.0-6.0)	0.698
Family income (IDR/mo.cap)	900 (600-1,333)	950 (525-1,650)	0.819
Dietary diversity score in the last 24-hour	4 (3-5)	4 (4-5)	0.891
Fish consumption in the last 24-hour (%)	36.0	20.0	0.116
Nutritional status			
Weight-for-length	-0.19±0.89	-0.22±0.81	0.878
Length-for-age	-1.86±0.94	-1.76±1.04	0.668
Weight-for-age	-1.03±0.94	-1.00±0.90	0.880
BMI-for-age	0.11±0.88	0.08±0.80	0.868
Hemoglobin	9.60±1.06	9.48±1.10	0.626
Developmental scores			
Mental Development Index (MDI)	97.0±8.8	96.6±10.6	0.855
Psychomotor Development Index (PDI)	98.7±14.6	98.6±18.4	0.993

[†]Values were mean ± standard deviation (SD) or median (25^{th},75^{th} percentiles).
[‡]Independent T-test.

Table 2. Results of linear regression analyses of rs 174468 SNP with plasma fatty acid concentrations and ratios[†]

Fatty acids (log)	Intercept	ß±SE[‡]	p-value
18:2 n-6 (LA)	1.69	-0.030±0.248	0.906
18:3 n-6 (gALA)	1.29	0.181±0.231	0.434
20:2 n-6 (Eicosadienoic acid)	0.483	-0.085±0.184	0.644
20:3 n-6 (DGLA)	-0.012	-0.067±0.158	0.672
20:4 n-6 (AA)	1.52	0.622±0.245	0.012
n-6 LC-PUFA	1.68	0.497±0.199	0.014
n-6 PUFA	2.29	0.218±0.145	0.135
18:3 n-3 (ALA)	1.19	-0.296±0.234	0.209
20:3 n-3 (ETA)	0.540	0.652±0.320	0.044
20:5 n-3 (EPA)	0.822	0.041±0.419	0.923
22:6 n-3 (DHA)	0.289	0.138±0.144	0.339
n-3 LC-PUFA	1.42	0.197±0.324	0.543
n-3 PUFA	1.90	0.023±0.228	0.918
LC-PUFA	2.04	0.323±0.236	0.174
PUFA	2.54	0.121±0.164	0.465
FADS1 index (AA:DGLA)	1.53	0.689±0.292	0.020
FADS2 index (DGLA:LA)	-1.70	-0.038±0.212	0.860
FADS2 index (DHA:EPA)	-0.534	0.098±0.351	0.781

[†]Genotype was scored as follow: GG=0, AG=1. [‡]Positive value indicates higher fatty acids in AG as compared to GG.

Table 3. Pearson correlation coefficients (*p*-value) between FADS indices and Mental Development Index (MDI)

FADS indices (log)	GG	AG
FADS 1	0.18 (0.858)	-0.436 (0.240)
FADS 2 (DGLA/LA)	-0.98 (0.317)	-0.273 (0.473)
FADS 2 (DHA/EPA)	0.15 (0.126)	0.648 (0.059)

Table 4. Multiple linear regression analysis of Mental Developmen Index (MDI) at 12-17mo[†]

Determinant	Coefficient B	95% CI	*p*
Intercept (constant)	99.16	96.8, 102	<0.001
Log FADS2 (DHA:EPA)	1.75	0.08, 3.41	0.040
Fish intake (last 24-hr)	-1.59	-5.03, 1.86	0.363
AG genotype[‡]	-0.50	-6.73, 5.74	0.875

[†]The final model explained 4.3% of the overall variation in MDI (n=115).
[‡]Homozygote for the major allele (GG) was set as reference.

comparable between the two genotypes of rs 174468 (GG and AG) and supports the previous finding of Morales that children who were breast-fed did not differ in their cognitive function score irrespective of genotype.[12] Similarly, Steer et al also reported that no genetic main effect with IQ was found for rs174575.[15] However, our finding was not in line with Caspi who suggested that the role of genetic variant was the determinant factor for the cognitive outcomes of children and reported that children carrying major allele of SNP (rs174575) had advantage in developmental score.[11] In the present study, we found only 2 genotypes (GG, AG) in the Sasak ethnics and the minor allele AG was found in <10% of the children. This is inline with finding from other Asian population (Chinese, Japanese) which found minor allele of SNP rs 174468 in only 1-2% of the subjects (http://www.ncbi. nlm.nih.gov/ projects/SNP/snp_ref.cgi?rs=174468).

The majority of the population in the Lombok Island are fishermen and most of them consume sea fish on regular basis. We found that 34.5% of the children and 59.7% of the mothers consumed fish within previous 24 hours, which suggests fish is common diet. Maternal fish consumption is reported to be associated with favourable child cognitive function[2,4] and most local people can afford it in the study area. Similarly, among the numerous short term and long term benefits of breast-feeding, cognitive development of children has been considered as one of the most consistently reported findings.[16] In the present study, we recruited only breast fed children and therefore it is reasonable to believe that the development of all the children should benefit from maternal fish consumption and breast-feeding. The mean MDI score of all the children (n=206) was 97.0±9.0 and we found that it is relatively comparable with mean MDI score of low socioeconomic Costa Rican infants i.e. was between chronic iron deficient and good iron status (93.1 vs 102.8, respectively) but was still lower than the mean of the middle socioeconomic children of both chronic iron deficient and good iron status (101 vs 109 respectively)[17] and was only two points lower than UK children at age 22 months i.e. 99.2±12.6.[18] Both of those studies and ours excluded low birth weight (LBW) and LBW was known to be associated with poorer cognitive function.[19]

FADS is a rate-limiting enzyme in the synthesis of LC-PUFA and polymorphism of FADS has been suggested to be crucial for the endogenous synthesis of LC PUFA.[6,20] It is widely accepted that carriers of minor alleles are associated with decline in desaturase expression or activity due to polymorphism. Koletzko et al has reported that carrier of minor alleles of FADS SNPs were negatively associated with LC-PUFAs and most notably of arachidonic acid (AA, 20:4 n-6) and EPA.[8] In the present study, we found that minor allele heterozygote (AG) of FADS SNP (rs1744658) was significantly associated with higher level of arachidonic acid AA (20:4 n-6), n-6 LC-PUFA, ETA and FADS1 index. Morales has reported that higher FADS2 index (DGLA:LA) which corresponds to low FADS1 index (AA:DGLA) is associated with child cognitive function score (MDI score).[12] We found a borderline significant association between FADS2 indices (DHA:EPA ratios) with MDI scores (r=0.648, p<0.059) in AG but not in GG genotype. The finding from multiple linear regression showed that MDI score was also associated with FADS2 index (DHA:EPA ratio). According to Morales, the child with higher FADS 1 index in the present study would have low cognitive function score but we did not find any significant difference of cognitive function score between the two genotypes. One of the possible explanations could be the fact that all the children in the present study were breast-fed and were able to achieve same cognitive function score. This finding supports the importance of breast-feeding during the early childhood.

Although lack of the homozygous AA genotype in the this study is in line with other studies from Asian countries,this study was done within a specific ethnicity in Indonesia (Sasaknese) and did not represent the multi-ethnicity population of Indonesia. All the children in the present study were still breast-fed and therefore we could not compare the findings in relation to breast-feeding status. Given the allele distribution, we found no minor allele homozygote (AA) which limited the statistical analysis and interpretation. Fish intake of the children was not quantified and this may limit the findings of the study. Finally, only one SNP rs 174468 was investigated in this study and further exploration of the genetic variations in FADS cluster among Indonesian children is necessary, including discovering potential new SNPs using new next generation sequencing of the FADS cluster. Given the small sample size in this study, replication with

bigger sample size needs to be conducted with other potential SNPs, preferably with more mixed ethnicities and birth weight categories. Despite these limitations, the study revealed the descriptive information about genotype of the Sasak ethnics in Indonesia in relation to fatty acid metabolism and the possible importance of FADS2 (DHA:EPA ratio) for child cognitive function.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Original Article

Genetic variants of FADS gene cluster, plasma LC-PUFA levels and the association with cognitive function of under-two-year-old *Sasaknese* Indonesian children

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FADS 基因簇的基因变异体、血浆 LC-PUFA 水平及其与印尼 Sasaknese 两岁以下儿童认知功能的关系

背景：长链多不饱和脂肪酸（LC-PUFA）被认为是儿童认知功能必不可少的。脂肪酸（FA）去饱和酶（FADS）的遗传变异被认为是 LC-PUFA 和儿童认知功能之间关系的重要效应调节剂。本研究旨在确定印尼 Sasaknese 两岁以下儿童中 rs174469 基因多态性遗传变异（基因型）的分布，并评估不同基因型下血浆 FA 和认知功能发展结果。**方法**：在印尼东部龙目岛地区进行随机试验收集基线资料（NUPICO，clinicaltrials.gov NCT01504633）。招募母乳喂养月龄为 12-17 个月的孩子，240 名对象被纳入本研究。采用贝利智力发育指数（MDI）评估儿童的认知功能。**结果**：收集到的 206 名受试者血样中，只发现两种基因型（90.3%GG 纯合子，9.7%AG 杂合子），并且次要等位基因 AG 与更高血液水平的花生四烯酸（20：4 n-6）、n-6 LC-PUFA 和 FADS1 指数显著相关。MDI 评分与 FADS2 指数（DHA：EPA）有关，但与基因型无关（调整后的 R^2=0.043）。**结论**：FADS2 指数与认知功能有关，这种关系在纯母乳喂养且非低出生体重基因型分别为 GG 和 AG 的婴儿中没有差别。

关键词：认知功能、FADS、印尼、LC-PUFA、两岁以下儿童