Effects of Early Maternal Docosahexaenoic Acid Intake on Neuropsychological Status and Visual Acuity at Five Years of Age of Breast-Fed Term Infants

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Objective We previously reported better psychomotor development at 30 months of age in infants whose mothers received a docosahexaenoic acid (DHA) (22:6n-3) supplement for the first 4 months of lactation. We now assess neuropsychological and visual function of the same children at 5 years of age.

Study design Breastfeeding women were assigned to receive identical capsules containing either a high-DHA algal oil (~200 mg/d of DHA) or a vegetable oil (containing no DHA) from delivery until 4 months postpartum. Primary outcome variables at 5 years of age were measures of gross and fine motor function, perceptual/visual-motor function, attention, executive function, verbal skills, and visual function of the recipient children at 5 years of age.

Results There were no differences in visual function as assessed by the Bailey-Lovie acuity chart, transient visual evoked potential or sweep visual evoked potential testing between children whose mothers received DHA versus placebo. Children whose mothers received DHA versus placebo performed significantly better on the Sustained Attention Subscale of the Leiter International Performance Scale (46.5 ± 8.9 vs 41.9 ± 9.3, $P < .008$) but there were no statistically significant differences between groups on other neuropsychological domains.

Conclusions Five-year-old children whose mothers received modest DHA supplementation versus placebo for the first 4 months of breastfeeding performed better on a test of sustained attention. This, along with the previously reported better performance of the children of DHA-supplemented mothers on a test of psychomotor development at 30 months of age, suggests that DHA intake during early infancy confers long-term benefits on specific aspects of neurodevelopment. *(J Pediatr 2010;157:900-5)*.

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Docosahexaenoic acid (DHA; 22:6n-3) is an important component of retinal and neural membranes and the intake of preformed DHA as a component of breast milk or as DHA-supplemented formula during infancy confers benefits with respect to visual acuity or neurodevelopment early in life.[1-6] However, optimal DHA intake during infancy has yet to be determined. The amount of this fatty acid in human milk is highly variable and dependent, in large part, on maternal DHA intake during lactation.[7,8] The mean DHA content of breast milk of U.S. women is considerably lower than that of women living in many other regions of the world, particularly regions in which fish intake is high.[7-12] Thus studies assessing the impact of different DHA intakes on visual function and neurodevelopment of both formula-fed and breast-fed infants should be useful in establishing optimal DHA intakes during early life.

We previously reported that formerly breast-fed children whose mothers received a DHA supplement of ~200 mg/d for 4 months postpartum had a significantly higher mean Bayley Psychomotor Development Index (PDI) at 30 months of age than children whose mothers received a placebo during the same period.[13] Because of this significant difference at 30 months of age, longer-term follow-up was thought to be warranted to track any ongoing psychomotor advantages resulting from early maternal DHA supplementation and to assess potential effects on other aspects of later neurodevelopment. A specific hypothesis was that children of supplemented mothers would be more attentive when evaluated at an age when this can be assessed more accurately than at 30 months of age.

DHA	Docosahexaenoic acid
K-ABC	Kaufman Assessment Battery for Children
PDI	Psychomotor Development Index
VEP	Visual evoked potential
WPPSI-R	Wechsler Primary and Preschool Scale of Intelligence-Revised

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Consequently, visual acuity and neuropsychological status were reevaluated at ~5 years of age.

Methods

As previously described,[13] pregnant women who planned to breast-feed exclusively for at least 4 months were assigned randomly in a double-blinded fashion to receive one of two identical capsules daily for 4 months, starting within 5 days after delivery. One of the capsules contained a high-DHA algal triglyceride (DHASCO; Martek Biosciences, Columbia, Maryland) consisting, by weight, of 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3); it provided ~200 mg of DHA daily. The other, the control capsule, contained a 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% α-linolenic acid (18:3 n-3).

The mothers were between 18 and 40 years of age, infant gestational age was >37 weeks, and infant birth weights were >2500 but <4200 g. None of the mothers had chronic disorders and none of the children had congenital anomalies, gastrointestinal tract symptoms or metabolic disorders. The same subjects were reevaluated at ~5 years of age at which time several measures of visual function and neurodevelopmental status were assessed and anthropometric variables were measured.

The study was approved by the Institutional Review Board for Human Subject Research of Baylor College of Medicine and Affiliated Hospitals and the Committee for the Protection of Human Subjects of the University of Texas Health Sciences Center at Houston. Written, informed consent was obtained from all mothers before enrollment and assent was obtained from each child before assessment at 5 years of age.

Assessment of Visual Function at 5 Years of Age

Binocular visual acuity was assessed using sweep visual evoked potential (VEP) and monocular visual acuity (each eye) was assessed using the ETDRS/Bailey-Lovie chart. Transient VEP testing also was performed and stereoacuity was assessed by the Titmus Fly Stereotest.[14] Details of the VEP methods have been described.[13,15] The ETDRS/Bailey-Lovie chart[16] has equal increments between lines of vision, equivalent complexity in letters per line and numbers of letters per line which provide some advantages over the traditional Snellen chart for this age group. The primary outcome metric is total number of letters identified correctly. If desired, visual acuity calculated using the ETDRS/Bailey-Lovie chart can be converted easily to Snellen equivalents. The Titmus Fly Stereotest, a contour stereotest that provides a measure of stereoacuity, was presented to each subject and the subject was asked to identify targets with varying stereoscoptic depth.

Assessment of Neurodevelopmental Status

The neurodevelopmental assessment battery used at 5 years of age was chosen to provide continued tracking of abilities assessed by the Bayley PDI which was higher in the supplemented group at 30 months of age, as well as to assess other functional domains that might be affected by DHA supplementation.

To track the positive effects on motor skills observed at 30 months of age (ie, a higher Bayley PDI), gross motor skills were assessed with the Leg Coordination subtest of the McCarthy Scales of Children's Abilities[17] and the Hand Movement subtest of the Kaufman Assessment Battery for Children (K-ABC)[18]; fine motor skills were assessed with the Purdue Pegboard Test[19] and the motor component of the Developmental Test of Visual-Motor Integration, Third Edition.[20] Overall cognitive level was assessed using the Information, Vocabulary, and Block Design subtests of the Wechsler Primary and Preschool Scale of Intelligence-Revised (WPPSI-R).[21] The Information and Vocabulary subtests provide a measure of verbal skills and the Block Design subtest of the WPPSI-R and the Developmental Test of Visual-Motor Integration, Third Edition, respectively, provide evaluation of perceptual and visual-motor skills. The Visual-Motor Integration test also allows decomposition of visual-motor skills into perceptual and motor components. Emerging executive function was assessed by the Animal Pegs subtest of the WPPSI-R and the Hand Movement subtest of the K-ABC. Visual attention was assessed with the Sustained Attention subtest of the Leiter International Performance Scale-Revised.[22] This test, which assesses attention and selectivity on repetitive tasks, requires the child to look at a target picture and, within a specified period of time, to mark each of the target pictures on a page containing both target and non-target pictures.

Each assessment instrument has its own age-dependent norms. All assessments were administered and scored by psychologists trained and experienced in their use according to the standardized protocol for each test.

Anthropometry

Weights of the children without shoes and heavy clothing were determined with an electronic integrating scale accurate to $\pm$ 0.1 kg. Height was measured with a wall-mounted stadiometer and head circumference was measured with a metal measuring tape.

Data Analysis

Data are expressed as group means $\pm$ standard deviation. The statistical significance of differences in continuous outcome variables between groups was tested by independent samples *t* tests (SPSS Software; SPSS, Chicago, Illinois).

Group differences in neurodevelopmental outcomes were further evaluated by analysis of covariance controlling for sex, ethnicity, maternal age, maternal education, maternal IQ (as determined by the Slosson Intelligence Test-Revised,[23] a screening test for intellectual abilities of adults), the composite score of the Family Environment Scale,[24] birth weight, and weight and height at the time of assessment. Correlations between selected outcome variables were assessed by linear regression analysis. The statistical significance of frequency

differences in categorical variables between groups was tested by the χ^2 statistic or Fisher exact test for small cell size. A probability of ≤5% was assumed to be statistically significant.

Results

The participants in the study through 30 months of age were reported.[13] Initially, each group included 115 infants. There were numerous dropouts from both groups during the first 4 months primarily because of limited breast milk intake or total cessation of breast-feeding. Only 83 subjects in the DHA-supplemented group and 77 in the control group were available for study at 30 months and by 5 years of age, 60 children in the DHA group, and 59 in the control group remained. All dropouts between 30 months and 5 years of age occurred because of relocation.

The two groups of mothers did not differ appreciably in mean age at delivery (31.3 ± 4 vs 32.0 ± 5 years in the supplemented and control groups, respectively), parity (1.8 ± 1 vs 1.7 ± 1), or years of education (16.5 ± 2.9 vs 16.1 ± 2.2). The demographic characteristics of the children in the two groups also did not differ significantly (Table I), and the demographic characteristics of mothers and infants remaining in the study at 5 years of age did not differ from those of the total group enrolled.

Visual Function

Results of transient VEP testing at a check size of 30′, nominally equivalent to 20/100 visual acuity, sweep VEP acuity, and the number of letters identified correctly with the ETDRS/Baily-Lovie chart are shown in Table II. There were no statistically significant differences between groups on any of these measures, and all were within the normal limits for age. In addition, all subjects correctly identified the smallest stereoscopic target (angle = 40 seconds of arc) on the Titmus Fly Stereotest.

Neurodevelopmental Outcomes

Neurodevelopmental outcome variables are shown in Table III. There were no differences between groups on measures of gross motor development, fine motor development, perceptual/visual-motor development, verbal skills, or emerging executive function. However, children whose mothers received the DHA supplement performed significantly better on the Sustained Attention subtest of the Leiter International Performance Scale-Revised (46.5 ± 8.9 vs 41.9 ± 9.3, P = .008). Adjusting for maternal IQ, scores on the home environmental assessment, as well as age at testing, sex, gestational age at birth, and maternal age did not affect the significance of this result. When stratified by sex, the difference between groups was statistically significant for girls (50.5 ± 9.1 vs 41.0 ± 9.6; P = .001) but not for boys (43.8 ± 7.8 vs 42.5 ± 9.1; P = .55). There was no significant correlation between the Sustained Attention subscore at 5 years of age and the Bayley PDI at 30 months of age. There also were no significant correlations between infant plasma phospholipid DHA content at either 4 or 8 months of age, measures of visual function at 5 years of age, or neurodevelopmental status at 5 years of age.

Table I. Characteristics of subjects completing the study through 5 years of age (mean ± SD)

	Algal DHA (n = 60)	Control (n = 59)
Birth weight (kg)	3.45 ± 0.50	3.49 ± 0.59
Gestational age at birth (wk)	39.4 ± 1.3	39.3± 1.5
Apgar score at 1 min	8.2 ± 1.0	8.2 ± 0.6
Apgar score at 5 min	9.0 ± 0.4	9.0 ± 0.3
Sex (% boys)	60%	57.6%
Ethnicity		
Caucasian	82%	76%
African American	12%	15%
Hispanic	5%	7%
Other	2%	2%
Age at testing (yr)	5.3 ± 0.3	5.3 ± 0.2
Weight at time of testing (kg)	19.9 ± 2.8	19.6 ± 2.5
Height at time of testing (cm)	112.4 ± 5.3	111.5 ± 5.5
Head circumference at time of testing (cm)	51.5 ± 0.9	51.4 ± 1.1

Anthropometry

There were no statistically significant differences in weight, length, or head circumference between the two groups at the time of testing, and all were within the expected ranges for age (Table I).

Discussion

We reported previously that maternal supplementation with approximately 200 mg of DHA per day for 4 months after delivery resulted in ~75% greater content of milk lipid DHA and ~35% greater DHA content in infant plasma phospholipids.[13] More important, the Bayley PDI of 30-month-old children whose mothers received the DHA supplement for only 4 months postpartum was 8.4 points (~0.5 SD) higher than that of children whose mothers received a placebo. We report here the results of visual and neurodevelopmental testing of the same cohort of children at ~5 years of age.

No differences between groups were observed on several measures of visual function or on several other neurodevelopmental domains. Transient VEP amplitude with 30′ check sizes was lower at 5 years of age in the DHA-supplemented

Table II. Visual acuity

	DHA	Placebo
VEP Latency* (msec)	110.3 ± 8.1 (n = 60)†	108.0 ± 6.5 (n = 56)†
VEP Amplitude* (μvolts)	39.6 ± 13.7 (n = 60)†	45.3 ± 18.0‡ (n = 56)†
Sweep VEP acuity (cyc/deg)	11.9 ± 0.3 octaves (n = 56)†	11.8 ± 0.3 octaves (n = 55) †
Bailey Lovie Acuity – right eye (no. of letters correct)	52.6 ± 4.6 (n = 60)†	51.6 ± 5.6 (n = 58)†
Bailey Lovie Acuity – left eye (no. of letters correct)	53.1 ± 4.7 (n = 60)†	52.1 ± 4.9 (n = 57)†

*Results using 30' check sizes.
†Number of subjects who completed each assessment or who had interpretable data from the assessment.
‡P = .06; P > .1 for all other comparisons.

Table III. Neuropsychological outcomes (mean ± SD) at 5 years of age

Assessment	Algal DHA	Control
K-ABC (Hand Movement)	8.39 ± 2.55 (n = 59) †	9.02 ± 2.84 (n = 56) †
McCarthy (Leg Coordination)	10.6 ± 1.5 (n = 59) †	10.7 ± 1.9 (n = 56) †
Purdue Pegboard Test		
Dominant Hand	9.6 ± 1.7 (n = 59) †	9.8 ± 2.7 (n = 57) †
Non-Dominant Hand	8.9 ± 1.6 (n = 59) †	8.9 ± 2.7 (n = 57) †
Developmental Test of Visual-Motor Integration, 3rd ed	11.6 ± 1.9 (n = 57) †	11.8 ± 1.8 (n = 56) †
Visual Component	14.8 ± 2.8 (n = 58) †	14.4 ± 2.6 (n = 56) †
Motor Component	11.6 ± 2.4 (n = 59) †	11.5 ± 2.7 (n = 56) †
Wechsler Primary and Preschool Scale of Intelligence – Revised:		
Animal Pegs Subset	12.1 ± 2.4 (n = 60) †	12.2 ± 1.8 (n = 57) †
Block Design Subset	11.3 ± 2.1 (n = 60) †	11.1 ± 2.2 (n = 57) †
Information Subset	10.8 ± 2.6 (n = 60) †	11.2 ± 2.6 (n = 57) †
Vocabulary Subset	12.3 ± 2.8 (n = 60) †	12.9 ± 2.4 (n = 56) †
Leiter (Sustained Attention)	46.5 ± 8.9 (n = 55) †	41.8 ± 9.3‡ (n = 55) †

K-ABC (Hand Movement), Hand Movement Subtest of the Kaufman's Assessment Battery for Children (raw score); *McCarthy (Leg Coordination),* Leg Coordination Subtest of the McCarthy Scales of Children's Abilities (raw score); *Leiter (Sustained Attention),* Sustained Attention Subtest of the Leiter International Performance Scale-Revised (raw score).
†Number in parentheses indicates number of subjects completing that assessment.
‡$P = .008$; $P > .1$ for all other comparisons.

versus control group (39.6 ± 13.7 vs 45.3 ± 18.0 μvolts), but the difference was of borderline statistical significance ($P = .06$). Transient VEP amplitudes at 4 and 8 months of age also were lower in the DHA versus the control group ($P < .03$).[13] However, the biologic or functional significance of this finding is not clear.

Because attentiveness is required to complete the Bayley PDI, it is tempting to speculate that the better performance of the supplemented group on the Bayley PDI at 30 months of age reflects better emerging attention (which is difficult to assess at 30 months of age) rather than better psychomotor development, per se. Although this is possible, it is not supported by other data. Specifically, there was no correlation between the sustained attention score at 5 years of age and the Bayley PDI at 30 months of age. Moreover, the difference between groups in performance on the Leiter Sustained Attention subscore was sex-dependent, being observed only in girls. The reason for this sex-related difference is not clear, but sex-related developmental differences have been seen in other studies, including a study in which DHA + γ-linolenic acid supplementation resulted in a higher Bayley Mental Development Index at 18 months corrected age in male, but not female, preterm infants.[25]

The study reported here is one of a very few assessing the impact of maternal omega-3 fatty acid supplementation during pregnancy or lactation on infant visual or neurodevelopmental outcomes. Cheruku et al[26] reported that infants of mothers with higher plasma phospholipid DHA concentrations had a lower ratio of active to quiet sleep, suggestive of a more mature sleep pattern. Ghys et al[27] found no association between cognitive development of 4-year-old term children and umbilical venous plasma or erythrocyte phospholipid DHA or arachidonic acid contents. A follow-up study demonstrated no association between cognitive performance at 7 years of age assessed by the Kaufman Assessment Battery for Children and DHA or arachidonic acid levels in either umbilical venous plasma phospholipids or plasma phospholipids at 7 years.[28] Another study showed that children whose mothers ate oily fish during pregnancy were more likely to have high-grade stereoacuity at 3.5 years of age than children whose mothers did not eat oily fish.[29] Better visual acuity at 2 and 12 months of age also was observed in breast-fed infants with higher erythrocyte phosphatidyl ethanolamine DHA content at 2 months of age,[4] as has statistically significant positive correlations between indexes of infant DHA status at 2 months of age and measures of language development at 9 and 18 months of age.[30]

A few interventional trials assessed the impact of maternal DHA intake during pregnancy on visual and neurodevelopmental outcomes. Malcolm et al[31] assigned women to receive either fish oil (~323 mg/d) or high oleic sunflower oil from 15 weeks gestation until delivery and assessed electroretinograms of the infants within the first week of life, as well as pattern-reversal VEP at 50 and 66 weeks postconceptional age. This low-dose DHA supplementation did not increase DHA levels of umbilical cord blood plasma or erythrocyte total lipids significantly, and there were no differences between groups in electroretinography or VEP measures. However, maturation of pattern-reversal VEP and retinal sensitivity correlated with DHA status; infants with higher DHA status had shorter VEP peak latencies (a positive finding).

Helland et al[6] assigned women in Norway to receive either a cod liver oil (~1200 mg DHA, ~800 mg eicosapentaenoic acid) or corn oil supplement from 18 weeks gestation through 3 months postpartum. Children whose mothers received the cod liver oil had a higher composite score on the Kaufman Assessment Battery for Children at 4 years of age.

Colombo et al[32] assessed the effects of maternal DHA status on development of attention during infancy and toddlerhood in children born to mothers participating in a DHA-supplementation trial. Infant control-habituation was assessed at 4, 6, and 8 months of age and free-play attention and distractibility were assessed at 12 and 18 months of age. Children whose mothers had a higher erythrocyte phospholipid DHA content at delivery had a more marked decline

in looking over the first year of life, suggesting better attention and less distractibility in the second year of life.

A few interventional studies assessed the effect of maternal DHA supplementation during lactation on infant visual and developmental outcomes. Gibson et al[33] assigned breastfeeding women to a placebo group (n = 12) or groups receiving 200 mg (n = 10), 400 mg (n = 12), 900 mg (n = 10), or 1300 mg (n = 8) of DHA per day for the first 12 weeks postpartum[33] and determined visual acuity of the infants at 12 and 16 weeks of age by VEP, as well as the Bayley Scales of Infant Development at 1 and 2 years of age. No relationship between visual acuity at either age tested and infant DHA status was detected. However, erythrocyte DHA status at 12 weeks of age was associated with a higher Bayley Mental Development Index at 1, but not 2, years of age.

Lauritzen et al[34] supplemented lactating Danish women who had low habitual intakes of omega-3 fatty acids with fish oil supplying 1.3 grams of long-chain omega-3 fatty acids per day vs the same amount of olive oil for the first 4 months postpartum and assessed visual acuity by sweep VEP at 2 and 4 months of age. Visual acuity did not differ significantly between groups at either age but, at 4 months of age, was positively associated with infant erythrocyte DHA content. Interestingly, in follow-up studies, children in the fish oil group had a lower passive vocabulary at 1 year of age than children in the olive oil group (with an inverse association between word comprehension at 1 year and erythrocyte DHA content at 4 months), but no difference between groups was found at 2 years of age.[35]

The precise periods during which adequate DHA is crucial for the developing retina and brain with respect to specific neurodevelopmental outcomes remain to be clarified. Our data, together with data from several of the studies mentioned above, suggest that early infancy is such a period. Furthermore, because DHA supplementation during pregnancy alone does not consistently increase breast milk DHA content,[36] adequate maternal DHA intake during lactation is warranted. Consumption of even very high amounts of the DHA precursor, α-linolenic acid, during pregnancy or lactation does not increase breast milk DHA content significantly.[37]

The biologic or "real-life" significance of an improvement in sustained attention of the magnitude observed in this study at 5 years of age is difficult to ascertain, particularly because scores of both groups were within the normal range for age. Nonetheless, this finding underscores the importance of longer-term follow-up studies of early DHA supplementation.

Although the mechanisms underlying long-term benefits of early nutritional interventions may not be well understood, delayed adverse neurologic effects have been documented with early nutritional deficits, such as iron deficiency during infancy.[38,39] Effects of higher DHA intake during infancy on blood pressure later in childhood also have been reported.[40] It is equally plausible that beneficial effects of early DHA intake on neurodevelopment may not be apparent until later in life or that early advantages in one developmental domain may enhance subsequent development of apparently unrelated domains.[41]

The possible influence of genetic factors on the interaction between diet and cognitive function also must be considered. This is illustrated by the recent observation that the impact of breastfeeding on childhood IQ is moderated by variation in FADS2 (delta-6-desaturase—one of the key enzymes involved in the conversion of precursor fatty acids to longer-chain, more unsaturated fatty acids such as DHA and arachidonic acid), with breastfeeding associated with higher IQ only in children with a specific variant.[42] Interestingly, an association between higher DHA status or intake during adulthood and a lower risk of dementia or a slower decline in cognitive function was reported.[43-47] Also, in a small clinical trial, supplementation with DHA and arachidonic acid for 90 days resulted in improvement of memory and attention in adults with cognitive dysfunction.[48]

The finding of better sustained attention at 5 years of age also is potentially noteworthy in view of the positive association reported by Colombo et al[32] between better maternal DHA status at birth and less distractibility during toddlerhood. Regardless of the mechanism(s), the higher PDI at 30 months of age and higher sustained attention score at 5 years of age in children whose mothers received DHA vs control for only the first 4 months postpartum suggests that DHA supplementation of breastfeeding women with low dietary n-3 fatty acid intakes may benefit the recipient infant, not necessarily during the intervention period but up to 5 years, or perhaps more, later. The same rationale may be applicable to the formula-fed infant. The DHA content of breast milk (0.35% of total fatty acids) achieved with the supplementation used in this study is similar to a recent estimate of worldwide mean breast milk DHA content (ie, 0.32%).[8] The results of this study suggest that increasing DHA intake from 0.2 to 0.35% of total fatty acids during early infancy may confer specific long-term neurodevelopmental advantages. ■

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