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Duration of long-chain polyunsaturated fatty acids availability in the diet and visual acuity

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KEYWORDS
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Abstract

Background: Little is known about the critical period during which the dietary supply of long-chain polyunsaturated fatty acids (LCPUFAs) may influence the maturation of visual cortical function in term infants.
Aim: To define the relationship between duration of dietary LCPUFA supply and visual acuity at 52 weeks of age.
Study design: Data from 243 infants who participated in four randomized clinical trials of LCPUFA supplementation of infant formula at a single research center were combined. The primary outcome was visual acuity at 52 weeks of age as measured by swept visual evoked potentials (sweep VEP).
Results: Longer duration of LCPUFA supply was associated with better mean acuity at 52 weeks of age (r=—0.878; p<0.001). The relationship between duration of dietary LCPUFA supply and sweep VEP acuity at 52 weeks was similar whether the LCPUFAs were provided via formula containing 0.36% DHA and 0.72% ARA or human milk. Duration of breast-feeding was associated with individual infants' sweep VEP acuity outcomes at 52 weeks (r=—0.286; p<0.005). The duration of LCPUFA supply during infancy has a similar relationship to sweep VEP acuity at 52 weeks in breastfed infants regardless of birth order.
Conclusion: A continued benefit from a supply of LCPUFAs is apparent in infants through 52 weeks of age, suggesting that the brain may not have sufficient stores of LCPUFAs from an early postnatal supply to support the optimal maturation of the visual cortex.
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1. Introduction

Long-chain polyunsaturated fatty acids (LCPUFAs) are found in high concentrations in the human brain and retina. They are naturally present in human milk with levels ranging from 0.05% to 1% docosahexaenoic acid (DHA) and from 0.1% to 0.9% arachidonic acid (ARA) in women who consume Western diets [1]. LCPUFAs are accreted primarily during the period of rapid brain and retinal maturation; i.e., during the last trimester out to at least two years of age [2].

The visual system (retina and brain) continues to mature throughout the first postnatal year [3–5] and unrestricted visual stimulation during this critical period is necessary for normal maturation to occur [6]. Infants who are deprived of normal visual experience during the first months of life, for example due to a congenital cataract or strabismus, experience altered patterns of visual cortical maturation and may suffer permanent visual disabilities [7–13].

In addition to visual experience, the developing visual system also depends on adequate nutrition to support its postnatal growth spurt. During the critical period of maturation, the quantity and diversity of LCPUFAs incorporated into neural membranes may influence the efficiency of nerve cell signaling [14–19], leading to permanent differences in the cytoarchitecture of the brain by affecting the process of synapse formation and elimination of supernumery synapses. Thus, availability of LCPUFAs in the infant diet may have long lasting effects on brain function.

Little is known about the critical period during which the dietary supply of LCPUFAs may influence the maturation of visual cortical function. Previous studies provide support for the importance of a dietary LCPUFA supply during an infant's first months of life; visual acuity at 12 months is correlated with dietary LCPUFA supply at 2 months and red blood cell-LCPUFA concentration at 4 months [20,21]. In addition, there is evidence for a continuing need for LCPUFAs in the diet throughout the first year of life; early weaning from a dietary supply of LCPUFAs results in sub-optimal visual acuity at 12 months [22]. However, no study has directly examined the influence of the duration of LCPUFA supply on visual cortical maturation. Here, we combine the data from four randomized clinical trials of LCPUFA supplementation of infant formula conducted within a single research center to examine the relationship between duration of dietary LCPUFA supply and sweep visual evoked potential (sweep VEP) acuity at 52 weeks of age.

2. Methods

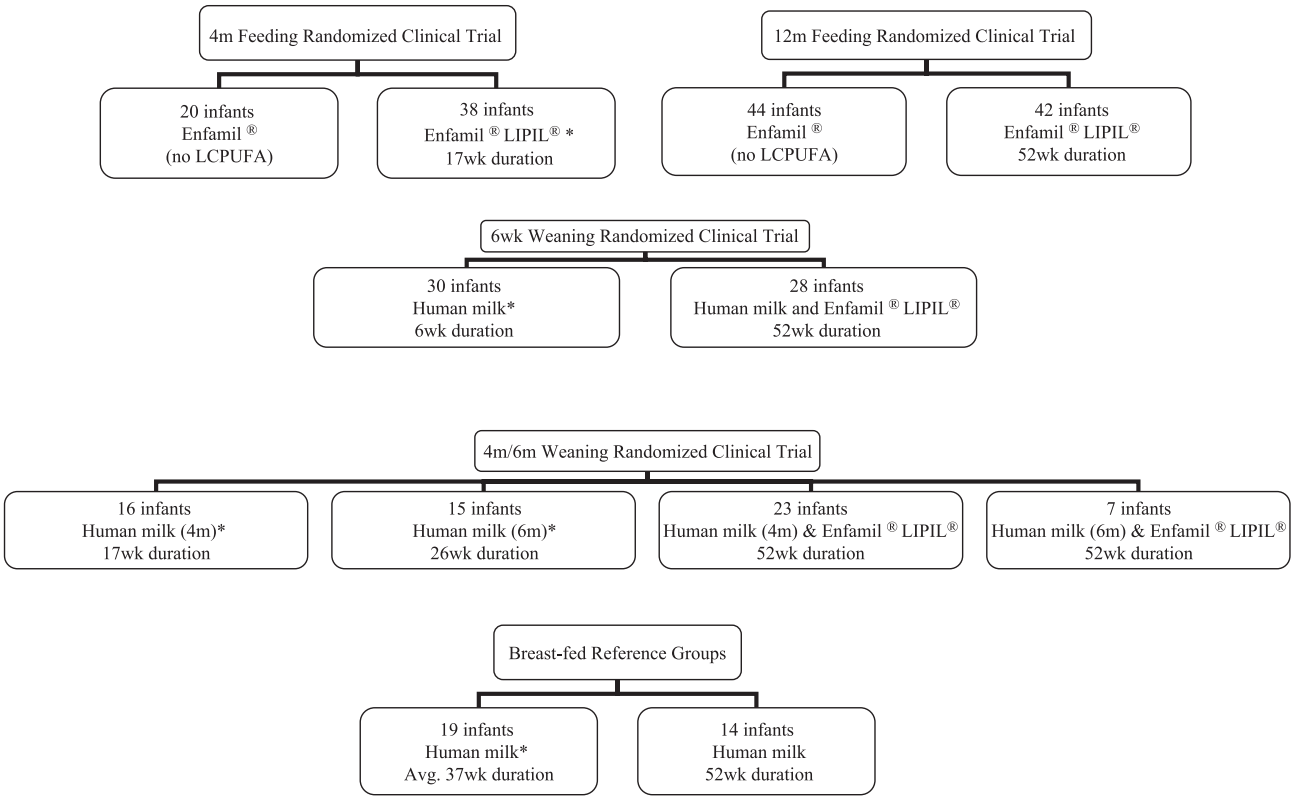
The analysis utilized data from four randomized controlled clinical trials conducted in our laboratory over the past 10 years [21–24]. An overall analysis of the data gathered in these trials was justifiable since inclusion and exclusion criteria (Table 1), infant formulas, and outcome measures were standardized across trials. Collectively, these trials enrolled 243 healthy term infants. The four trials observed the tenets of the Declaration of Helsinki and were approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center (Dallas), Presbyterian Hospital (Dallas) and Medical City Hospital (Dallas). Details of the consent and enrollment procedures for each trial have been published previously [21–24].

In two of the trials [21,24], infants were randomized at 0–5 days of age to receive either Enfamil® with Iron or Enfamil® LIPIL® with Iron (0.36% DHA, 0.72% ARA); infants were fed the assigned diet through 17 or 52 weeks of age. These trials were conducted between 1993–1996 and 1997–1999, respectively. In the other trials [22,23], infants were initially breast-fed but, at the time of weaning, were randomized to either Enfamil® with Iron or Enfamil® LIPIL® with Iron; infants were weaned at 6, 17, or 26 weeks of age. These trials were conducted between 1996–2000. We also utilized the data from two reference groups of breast-fed healthy term infants who were tested concurrently with the clinical trials; infants in these two groups were exclusively breast fed for an average of 37 ± 3 weeks or for a minimum of 52 weeks. These reference groups were evaluated during 1993–1996 and 1996–2000, respectively. Taken together, the four randomized clinical trials and two breast-fed reference groups yielded 12 groups of infants with varying sources and durations of LCPUFA dietary supply (Fig. 1).

Table 1 Inclusion and exclusion criteria[a]

Eligibility criteria
Born at 37–40 weeks post-conception as determined by sonogram, date of last menstrual period, and physical and neural development assessment at birth.
Singleton
Birth weight appropriate for gestational age
Exclusion criteria
Family history of milk protein allergy
Genetic or familial eye disease
Vegetarian or vegan maternal dietary patterns
Maternal metabolic disease, anemia, or infection, jaundice
Perinatal asphyxia
Meconium aspiration
Any perinatal event that resulted in placement of the infant in the neonatal intensive care unit

[a] Inclusion/Exclusion criteria were identical for all trials.



*Followed by formula containing no LCPUFA.

Figure 1 Summary of infant diet groups. All groups resulted from the conduct of four randomized controlled clinical trials (RCTs) within a single laboratory over the past 10 years. All RCTs had consistent inclusion/exclusion criteria, infant formulas, and outcome measures. The RCTs included a 4-month feeding trial [21], a 12-month feeding trial [24], a 6-week weaning trial [22], and a 4-month/6-month weaning trial [23]. We also utilized the data from two reference groups of breast-fed healthy term infants who were tested concurrently with the RCTs; infants in these two groups were exclusively breast fed for an average of 37 weeks or for a minimum of 52 weeks.

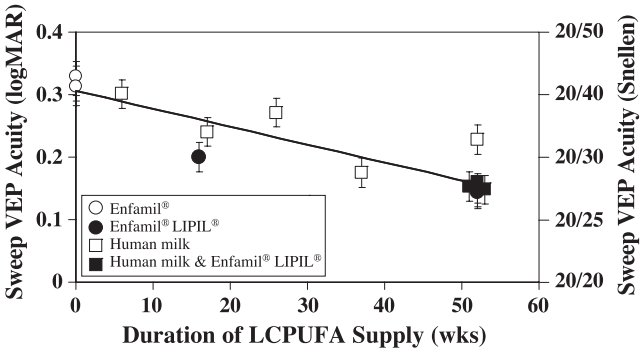


Figure 2 Duration of dietary LCPUFA supply and mean 52 week sweep VEP acuity for each diet group. Diet groups who were exclusively formula-fed are shown as circles; diet groups who were breast-fed for 6 weeks to 1 year are shown as squares. Diet groups who received no formula with LCPUFA are shown as open symbols; diet groups who received formula with LCPUFA (0.36% DHA, 0.72% ARA) are shown as filled symbols. Note that the data points at 0 week duration correspond to the two infant groups who received formula containing no LCPUFAs from birth to 52 weeks of age.

The primary outcome measure for all four trials was sweep VEP acuity at 52 weeks of age, when visual cortical function approaches maturity [25,26]. Details of this test protocol have been published previously [25,26]. Briefly, the sweep VEP records the visual cortical response to a contrast-reversing (6 Hz) black and white grating swept from coarse to fine (low to high spatial frequency). The finest grating that elicits a cortical response determines visual acuity and is reported as logMAR (minimum angle of resolution). Lower logMAR values represent better visual acuity.

3. Data analysis

The relationship between sweep VEP acuity outcome at 52 weeks and duration of LCPUFA supply was examined across all diet groups via linear regression of mean sweep VEP acuity in logMAR for each diet group on duration in weeks. Mean acuities entered into the regression were not weighted by sample size (since most sample sizes ranged from 15 to 40 infants for most diet groups) nor by the standard error of the mean (since sweep VEP acuity tests were conducted in a single center using standardized methods and standard errors were comparable for all randomized diet groups and for most breast-fed reference group infants). The relationship between sweep VEP acuity outcome at 52 weeks and duration of LCPUFA supply was examined across breast-fed infants via linear regression of individual sweep VEP acuities in logMAR on duration in weeks.

4. Results

Mean visual acuity outcome at 52 weeks is plotted as a function of duration of LCPUFA supply in Fig. 2. Note that the data points at 0 week duration correspond to the two infant groups who received formula containing no LCPUFAs from birth to 52 weeks of age. Other groups shown in Fig. 2 include infants who were fed Enfamil® LIPIL® for either 17 or 52 weeks, infants who were exclusively breast-fed for 6, 17, 37, or 52 weeks and infants who were breast-fed initially and then weaned at 6, 17, or 26 weeks to Enfamil® LIPIL®. A longer duration of a dietary supply of LCPUFAs, regardless of whether it was obtained though human

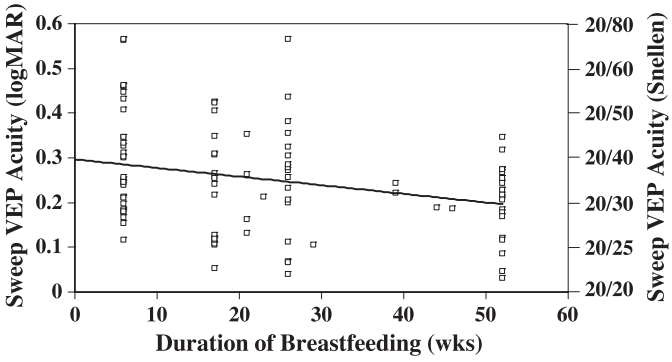


Figure 3 Duration of breast-feeding and individual 52 week sweep VEP acuity.

milk or formula, resulted in better visual acuity at 52 weeks (slope=−0.003 logMAR/week, r=−0.878; $p<0.001$). Similar results were obtained when the analysis was limited to infants who received LCPUFAs solely through breast-feeding (slope=−0.002 logMAR/week) or solely through formula feeding (slope=−0.003 logMAR/week). In practical terms, this means that infants who received a supply of LCPUFA for 36 weeks of life have visual acuity that is, on average, 0.1 logMAR better than infants who receive no LCPUFAs in their diet (i.e., their visual acuity is better by about one full line on an eye chart). As another example, infants who received a supply of LCPUFAs for an entire 52 weeks had visual acuity 0.14 logMAR better than infants who received no LCPUFAs, equivalent to about 1.5 lines better on an eye chart.

We evaluated whether there was a plateau in the relationship between duration of breastfeeding and visual acuity outcome statistically by comparing a linear model and a bilinear model of the data. The linear model describes continued benefit of LCPUFA supply up to 52 weeks of age; the bilinear model describes an early period of benefit followed by a plateau in which there is no further benefit of continuing LCPUFA supply. The bilinear model did not provide a significantly better fit to the data than the linear model (chi-square (2)=1.86, p=0.3944), consistent with the absence of a plateau. That is, the statistical analysis supports a continued benefit from a supply of LCPUFAs up to at least 52 weeks of age.

Fig. 3 shows the individual data from breast-fed infants whose mean acuities were plotted as open squares in Fig. 2. Although there is a fair amount of scatter in the data, about +/−1 line of visual acuity on an eye chart, there is a significant correlation between duration of breast-feeding and visual acuity at 52 weeks (slope=−0.002 logMAR/week; r=−0.286; $p<0.005$; n=94).

There is some evidence that maternal LCPUFA status may be reduced during pregnancy and lactation so that primiparous (firstborn) infants may receive more LCPUFA in utero than multiparous infants [27]. The relationship between duration of breast-feeding and 52 week visual acuity in 39 primiparous infants (slope=−0.002 logMAR/week, r=−0.308; $p<0.05$) was similar to that for 55 multiparous infants (slope=−0.002 logMAR/week, r=−0.277; $p<0.05$).

5. Conclusions

The duration of dietary LCPUFA influences the maturation of sweep VEP acuity. The effect of duration results in a difference in visual acuity at 52 weeks of age equivalent to 1.5 lines on a standard eye chart between infants who never received LCPUFAs in their diet and infants who received LCPUFAs throughout the first year of life. These differences in visual function may provide an important clue to the nutritional requirements of the developing central nervous system during a critical period of development. Indeed, alterations in fatty acid composition can have direct membrane effects on neural receptors, pumps, and channel signaling [14–19]. Resulting differences in nerve cell signaling during infancy could lead to permanent changes in the cytoarchitecture of the brain by affecting the processes of synapse formation and elimination of supernumerary synapses during a critical period [4,5].

The relationship between duration of dietary LCPUFA supply and sweep VEP acuity at 52 weeks was similar whether the LCPUFAs were provided via formula containing 0.36% DHA and 0.72% ARA or human milk. The similarity of visual acuity outcomes at 52 weeks among infants who received LCPUFAs for the entire year either from breast-feeding, formula with LCPUFAs, or breast-feeding followed by post-weaning formula containing LCPUFAs, supports the equivalent efficacy of these dietary sources. Going a step further, we suggest that these data support a sweep VEP acuity level of 0.157±0.081 logMAR (20/29 mean Snellen equivalent) as a possible functional standard to judge sufficiency of LCPUFA supply during the first year of life. Adoption of a common functional outcome standard would permit objective assessment of equivalent efficacy among infant formulas that provide different amounts of LCPUFAs and their parent fatty acids.

Interestingly, infants showed a continued benefit from a supply of LCPUFAs even up to 52 weeks of age, suggesting that the brain may not have sufficient stores of LCPUFAs from an early postnatal supply to optimally support the continued maturation of the visual cortex. This finding is consistent with previous studies which have also shown that duration of breastfeeding beyond 6 months of age correlates with higher developmental scores [28,29].

Data from individuals plotted in Fig. 3 illustrate the variability of sweep VEP acuity outcomes at 52 weeks of age among breast-fed infants. Some of this variability may reflect the variation in the concentration of LCPUFAs present in human milk among women who consume Western diets [1]. An earlier study demonstrated

a relationship between infant human milk DHA intake and sweep VEP acuity at 4 months of age [30].

Finally, the duration of LCPUFA supply during infancy has a similar relationship to sweep VEP acuity at 52 weeks in breastfed infants regardless of birth order. Multiparous infants, since they are likely to receive less LCPUFAs in utero, might be expected to show a different relationship between post-natal LCPUFA supply and visual acuity at 52 weeks than primiparous infants. This suggests that duration of post-natal LCPUFA supply may be more important than small variations in pre- and post-natal concentrations.

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