Dietary Essential Fatty Acid Supply and Visual Acuity Development

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The influence of dietary ω-3 fatty acid supply on visual acuity development was evaluated in very low birth weight (VLBW) infants using visual-evoked potential (VEP) and forced-choice preferential-looking (FPL) procedures at 36 and 57 wk postconception. The VLBW infants born at 27–33 wk postconception were randomized to one of three diet groups: corn oil, which provided solely linoleic acid; soy oil, which provided linoleic and α-linolenic acids; or soy/marine oil; which was similar to the soy oil formula but also provided preformed long chain ω-3 fatty acids. The VLBW infants in the soy/marine oil group had higher ω-3 levels in erythrocyte membranes and better VEP and FPL acuities at 36 and 57 wk than infants in the corn oil group. The soy oil group had intermediate ω-3 levels in erythrocyte membranes and significantly poorer VEP acuity at 57 wk compared with the soy/marine oil group. Only the soy/marine oil group had acuities comparable to the “gold standards” of VLBW infants fed human milk and preterm infants who were born and tested at 35–36 wk postconception. In addition, VEP and FPL acuity were poorer in a nonrandomized group of formula-fed full-term infants than in breast-fed full-term infants. The results suggest that dietary ω-3 fatty acid supply may play an important role in early human visual development. Invest Ophthalmol Vis Sci 33:3242–3253, 1992

During the third trimester of human fetal growth, the whole-body daily accretion rate of essential fatty acids (EFAs) averages 400 mg/kg body weight for the ω-6 series and 50 mg/kg for the ω-3 series.1 Because all vertebrates lack the desaturating enzyme necessary to form the ω-6 and ω-3 series of EFAs,2,3 preterm infants must rely on dietary sources to obtain them. With a dietary supply of the parent EFAs (ie, linoleic acid [18:2 ω-6] and α-linolenic acid [18:3 ω-3]), liver and brain microsomes can elongate and desaturate the EFAs further, generating a family of long-chain polyunsaturated fatty acids (LCPUFAs) for both the ω-6 and the ω-3 series. By comparison with the body as a whole, brain levels of the parent EFAs remain relatively stable during late gestation in humans, but LCPUFAs show dramatic increases during the third trimester and continue to rise postnatally.4,5

Docosahexaenoic acid (DHA or 22:6 ω-3) is an ω-3 LCPUFA that constitutes only a small percentage of total fatty acids in most human tissue lipids, but it is present in high levels in the retina, cerebral cortex, and spermatozoa.6 In the retina, the highest concentration of DHA is localized in the photoreceptor outer segments, which have an unusually high degree of membrane fluidity.7–12 In addition, studies with model membrane phospholipid bilayers suggest that optimal activity of rhodopsin may depend on the presence of DHA.13,14 Among subcellular fractions of the brain, the highest concentrations of DHA occur in the metabolically active and highly fluid membranes of synaptic vesicles.15,16

Intrauterine (maternal) and postnatal dietary supply of EFAs have been shown to affect infant rhesus monkey retina and brain fatty acid content and composition. In particular, decreased accretion rates of ω-3 derivatives have been found with high linoleic acid, α-linolenic acid-poor diets.17,18 These biochemical changes were accompanied by altered electroretinographic responses and reduced visual acuity.17–19 Dietary supplementation with DHA restored the fatty acid composition of the adult primate retina, but the electroretinogram remained abnormal.12

In the normal human full-term infant, the last trimester and early postnatal months are noted for high DHA accretion rates15,16 and rapid development of photoreceptors20–22 and visual cortex.23,24 Human preterm infants, however, may be vulnerable to bio-
chemical and functional consequences of DHA deficiency because they are deprived of the last trimester of intrauterine nutrition and have a reduced ability to elongate and desaturate the parent EFAs. Availability of ω-6 and ω-3 fatty acids in the diet of the healthy preterm infant has been shown to affect the relative content of ω-3 and ω-6 LCPUFAs in plasma and erythrocyte lipids. Diets low in ω-3 fatty acids also reduce the sensitivity and maximum amplitude of the rod photoreceptors in the healthy preterm infant. These data suggest that dietary ω-3 LCPUFA deficiency is associated with a rate of acuity development comparable to full-term norms but below that of ω-3 LCPUFA-supplemented preterm infants at some ages.

We evaluated whether the ω-3 EFA content of preterm formula affected visual acuity development in a homogeneous population of healthy very low birth weight infants. Visual-evoked potential (VEP) and preferential-looking methods were used to measure visual acuity in a group of infants who were assigned randomly to receive one of three diets from 10 days postnatal to 57 wk postconception. In addition, the acuities of the randomized groups were compared with acuities obtained from two nonrandomized “gold standard” dietary groups of preterm infants, a human milk-fed group and an intrauterine nurtured group. Finally, the interaction of gestational age at birth and dietary ω-3 fatty acid on visual acuity development was examined by comparison with acuities from two nonrandomized groups of full-term infants: human milk fed and formula fed.

Materials and Methods

Subjects

Participants in the randomized-formula study were 73 healthy preterm infants (41 girls and 32 boys) born at 27–33 wk postconception. The gestational age at birth was determined by clinical assessment. Their birth weights were 1000–1500 g, and they were appropriate for gestational age. None of the participants received respirator treatment for more than 7 days or had congenital infections, gross congenital malformations, retinopathy of prematurity, or grade III or IV intracranial hemorrhages (one patient had grade I and two had grade II; on follow-up, all participants had normal sonograms). Participants were randomized to one of three formula groups by 10 days of life: corn oil, soy oil, or soy/marine oil (details of the formulas are discussed subsequently). Clinical care, acuity evaluation, and fatty acid analysis were conducted without knowledge of dietary group assignment.

Nonrandomized participants were recruited to provide information about visual development under several gold-standard dietary regimens. These included ten healthy preterm infants (six girls and four boys) who met all the same criteria as the participants in the randomized formula study but who received at least 75% of their diet from human milk (preterm human milk group). Second, ten healthy preterm infants who were born at 35–36 wk gestation were recruited to provide information about acuity development in infants receiving intrauterine nutrition up to the 36 wk postconception target age for visual acuity testing (intrauterine group). Finally, 14 full-term infants (5 girls and 9 boys) who were fed only commercial formula (full-term formula group) and 35 infants (20 boys and 15 girls) who received 100% human milk through 2 mo postterm and at least 75% human milk through 4 mo postterm (full-term human milk group) were recruited.

The mean gestational ages at birth and birth weights for each group are given in Table 1. The corn oil, soy oil, soy/marine oil, and preterm human milk groups had equivalent gestational ages and birth weights. The intrauterine group contained only infants born at 35–36 wk postconception. The full-term formula and full-term human milk groups included only infants born at 39–41 wk gestation.

Testing was conducted at target ages of 36, 57, or 66 wk postconception. Mean postconceptional and postnatal ages at the time of each acuity test are given in Table 1 with the mean weights. All preterm infant groups were matched for postconceptional age and weight. Randomized preterm formula groups also were matched for postnatal age. Full-term groups were matched with preterm groups on the basis of postconceptional age (57–58 wk) or postnatal age (26–27 wk). There were no significant differences in weight among groups at the 36 wk or 57 wk test ages. The parents were informed of the nature of the study, and written consent was obtained in all cases.

Diets

Randomized preterm infants were assigned to one of three diets. Corn oil, based on medium-chain triglyceride (MCT), coconut oil, and corn oil, provided solely linoleic acid (18:2 ω-6) as EFA and corresponded to the 1987 formulation of Enfamil Premature (Mead Johnson, Evansville, IN). Soy oil, based on MCT, coconut oil, and soy oil, provided 18:2 ω-6 and 18:3 ω-3. Soy/marine oil, an experimental product similar to the soy oil formula but supplemented with marine oils, provided DHA (0.4%) similar to that
found in preterm human milk. Both premature and follow-up formulas were available. The EFA content of these formulas is given in Table 2, along with the EFA content of human milk and of full-term formula (Similac; Ross Laboratories, Columbus, OH).

Fatty Acid Analysis

Blood samples were obtained from randomized infants and preterm human milk group infants by venipuncture from a small arm vein at entry and at target dates of 36 and 57 wk postconception. The fatty acid composition of erythrocyte membranes served as an index of neural membrane fatty acid composition. Lipids were extracted and total fatty acid methyl esters prepared as previously described. Fatty acid methyl esters were separated and quantified by capillary gas chromatography. Relevant to our study was the ratio of end products of co-3 and co-6 desaturation (22:6 co-3/22:5 co-6); this ratio provided a measure of dietary ω-3 sufficiency.

VEP Acuity

Infants were held by a research nurse (preterm infants) or parent (full-term infants) 50 cm from a video monitor that presented high-contrast black and white checkerboard pattern-reversal stimuli. Responses were obtained from an active electrode placed 1 cm above the inion (V1), a reference electrode 30% of the nasion–inion distance (V2), and a ground electrode at the vertex. The potential difference (V2 – V1) was amplified (gain, 10,000; –3 dB cutoff at 0.1 and 30 Hz). An observer activated recording by pressing a foot pedal when the infant was alert and gaze was directed at the monitor. A thin colorful plastic bangle bracelet dangling in front of the video monitor and music boxes were used to help maintain attention. A contrast reversal rate of 3.8/sec was used to elicit responses to checks with sides subtending 214, 107, 54, 27, or 14 min of arc. All responses were recorded on FM tape (A. R. Vetter Co., Rebersburg, PA) and subsequently analyzed off-line on a PDP 11/73 computer (Digital Equipment Corp., Atlanta, GA). Responses (30–100 responses per check size) were filtered digitally at the reversal rate. Responses containing movement artifacts were rejected with a software subroutine. Peak-to-peak amplitude and phase were determined for each check size. Phase was converted to latency by a published method. Check size was adjusted to reflect the power in the diagonal component (150, 75, 38, 19, or 10 min of arc). The VEP acuity was derived from best-fit linear functions relating amplitude to the logarithm of adjusted check size (logMAR).

Table 2. Essential fatty acid content of human milk and study formulas

<table>
<thead>
<tr>
<th>Diet</th>
<th>Linoleic 18:2 ω-6</th>
<th>α-Linolenic 18:3 ω-3</th>
<th>ω-3 LCPUFAs 20:5 ω-3 and 22:6 ω-3</th>
<th>Total ω-6/ω-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human milk</td>
<td>12.7*</td>
<td>0.8</td>
<td>0.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Premature (corn oil)</td>
<td>24.2</td>
<td>0.5</td>
<td>0.0</td>
<td>48.4</td>
</tr>
<tr>
<td>Premature (soy oil)</td>
<td>20.8</td>
<td>2.7</td>
<td>0.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Premature (soy/marine)</td>
<td>20.4</td>
<td>1.4</td>
<td>1.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Follow-up (corn oil)</td>
<td>21.1</td>
<td>0.5</td>
<td>0.0</td>
<td>43.1</td>
</tr>
<tr>
<td>Follow-up (soy oil)</td>
<td>20.3</td>
<td>2.8</td>
<td>0.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Follow-up (soy/marine)</td>
<td>18.1</td>
<td>1.4</td>
<td>0.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Full-term formula</td>
<td>29.4</td>
<td>0.8</td>
<td>0.0</td>
<td>36.8</td>
</tr>
</tbody>
</table>

* Expressed as g/100 g lipids. Corn oil- and soy oil-based formulas contained no ω-3 long-chain polyunsaturated fatty acids (LCPUFAs).
Table 3. Mean (± standard deviation) LCPUFA content of erythrocyte membranes

<table>
<thead>
<tr>
<th>Diet</th>
<th>At entry</th>
<th></th>
<th>36 wk postconception</th>
<th>57 wk postconception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LCPUFA w-6</td>
<td>LCPUFA w-3</td>
<td>LCPUFA w-6</td>
<td>LCPUFA w-3</td>
</tr>
<tr>
<td>Human milk</td>
<td>22.95*</td>
<td>5.86</td>
<td>21.85</td>
<td>7.64*</td>
</tr>
<tr>
<td></td>
<td>(5.47)</td>
<td>(1.64)</td>
<td>(7.04)</td>
<td>(3.48)</td>
</tr>
<tr>
<td>Corn oil</td>
<td>21.36</td>
<td>4.76</td>
<td>24.00</td>
<td>4.39†</td>
</tr>
<tr>
<td></td>
<td>(5.69)</td>
<td>(1.29)</td>
<td>(5.72)</td>
<td>(1.23)</td>
</tr>
<tr>
<td>Soy oil</td>
<td>24.08</td>
<td>5.48</td>
<td>24.58</td>
<td>5.85§</td>
</tr>
<tr>
<td></td>
<td>(6.48)</td>
<td>(1.87)</td>
<td>(4.57)</td>
<td>(1.39)</td>
</tr>
<tr>
<td>Soy/marine oils</td>
<td>23.56</td>
<td>5.51</td>
<td>23.23</td>
<td>7.93†</td>
</tr>
<tr>
<td></td>
<td>(6.82)</td>
<td>(1.99)</td>
<td>(3.30)</td>
<td>(1.71)</td>
</tr>
</tbody>
</table>

* Expressed as g/100 g lipids.
†‡§ Reading down a column, means with different superscripts are significantly different by analysis of variance.

Forced-Choice Preferential Looking (FPL) Acuity

Binocular grating acuity was evaluated using handheld Teller acuity cards and a 2-down, 1-up staircase procedure. Infants were held by a research nurse (preterm infants) or parent (full-term infants) 57 cm from the position where cards were presented. On each trial, the infant was confronted with an acuity card. The tester viewed the infant through a peephole in the card and, without knowledge of the spatial frequency of the grating or its position on the card, made a forced-choice judgment about which side the infant preferred. The card then was reversed to present the grating in the opposite position, and the tester made a second judgment. The examiner handed the card to an assistant who noted results on a score sheet and selected the appropriate next card. The initial location of the grating was randomized across cards. Cards were available in approximate half-octave spatial frequency steps. Eight staircase reversals were obtained and acuity was calculated as the logMAR average of the eight reversal points.*

Statistical Analyses

Two separate one-way analysis of variance tests were done to assess the effects of diet on visual acuity development among randomized formula groups and among the combined randomized and gold-standard groups. A two-way analysis of variance was conducted to assess the main effects of gestational age at birth and diet and their interaction on visual acuity development among preterm and full-term infants. All post hoc comparisons between diet groups were conducted using the Newman-Keuls test.

Results

Randomized Preterm Formula Groups at 36 Wk Postconception

The mean LCPUFA content in erythrocyte lipids for each of the randomized preterm formula groups at three test dates is given in Table 3. At entry, there were no significant differences among groups in ω-6 or in ω-3 LCPUFAs. However, by 36 wk postconception, all three groups were significantly different in ω-3 LCPUFAs (F = 16.6, P < 0.001). The corn oil group had the lowest levels, and the soy/marine oil group the highest levels.
group had the highest \( \omega-3 \) LCPUFA levels. No significant differences in \( \omega-6 \) LCPUFAs were found (\( F = 0.7 \), not significant).

Mean VEP acuity at 36 wk postconception is shown for each of the three randomized formula groups in Figure 1. There was a significant effect of formula group on VEP acuity (\( F = 3.88, P < 0.025 \)). Post hoc tests showed that the corn oil group had significantly poorer VEP acuity than the soy/marine oil group (\( P < 0.05 \)). The VEP acuity was correlated with the end-product ratio, \( 22:6 \omega-3/22:5 \omega-6 (r = -0.26, P < 0.05) \).

Randomized Preterm Formula Groups at 57 Wk Postconception

At 57 wk postconception, all three groups were significantly different in \( \omega-3 \) LCPUFAs (\( F = 21.6, P < 0.001 \)). The disparity between the corn oil group and the soy/marine oil group had increased since 36 wk postconception (Table 3). Unlike the 36-wk data, at 57 wk, there was also a significant difference in \( \omega-6 \) LCPUFAs. The soy/marine oil group had significantly lower levels than the corn oil and soy oil groups (\( F = 13.1, P < 0.001 \)).

Mean VEP and FPL acuities at 57 wk postconception are shown for each of the three randomized formula groups in Figure 1. There was a significant effect of formula group on VEP acuity (\( F = 7.59, P < 0.002 \)). Post hoc tests showed that both the corn oil group (\( P < 0.05 \)) and the soy oil group (\( P < 0.05 \)) had significantly poorer VEP acuity than the soy/marine oil group. The VEP acuity was correlated with the end-product ratio, \( 22:6 \omega-3/22:5 \omega-6 (r = -0.50, P < 0.001) \). Overall, there was a borderline effect of formula group on FPL acuity (\( F = 2.99, P < 0.061 \)). Post hoc tests showed that the corn oil group had significantly poorer FPL acuity than the soy/marine oil group.
group \((P < 0.05)\). In addition, FPL acuity was correlated with the end-product ratio, 22:6 \(\omega-3/22:5 \omega-6\) \((r = -0.34, P < 0.05)\).

**Comparison With Preterm Human Milk and Intrauterine Groups**

VEP and FPL acuity histograms for the preterm human milk and intrauterine groups tested at 36 and 57 weeks post-conception.
57 wk postconception are shown in Figure 2. The preterm human milk group and intrauterine group logMAR acuities were distributed normally (Kolmogorov-Smirnov P value range, 0.78–0.98), and the solid curves represent the best-fit normal distribution for each measure. These data provide a gold standard for optimal visual development in preterm infants.

Frequency histograms of acuities obtained from the corn oil, soy oil, and soy/marine oil preterm groups are shown in Figures 3–5 with the gold-standard distributions. Overall, there was a significant effect of diet on VEP acuity at 36 wk (Fig. 3, F = 5.02, P < 0.001). Post hoc tests showed that the corn oil group had significantly poorer VEP acuity than the soy/marine oil group (P < 0.05), the preterm human milk group (P < 0.05), and the intrauterine group (P < 0.05). In addition, the soy oil group had poorer VEP acuity than the preterm human milk group (P < 0.05). For all preterm groups, including the preterm human milk group and the randomized formula groups, VEP acuity was correlated with the fatty acid content in erythrocyte membranes, specifically the end-product ratio, 22:6ω-3/22:5ω-6 (r = -0.23, P < 0.05).

A significant effect of diet on VEP acuity also was found at 57 wk (Fig. 4, F = 5.85, P < 0.002). Post hoc tests showed that the corn oil group had significantly poorer VEP acuity than the soy/marine oil group (P < 0.05) and the preterm human milk group (P < 0.05). In addition, the soy oil group had poorer VEP acuity than the soy/marine oil group (P < 0.05). Including the preterm human milk group along with the randomized formula groups, VEP acuity was correlated with the end-product ratio, 22:6ω-3/22:5ω-6 (r = -0.52, P < 0.001). There was a significant effect of diet on FPL acuity at 57 wk (Fig. 5, F = 3.67, P < 0.019). Post hoc tests showed that the corn oil group had significantly poorer FPL acuity than the soy/marine oil group (P < 0.05) and the preterm human milk group (P < 0.05). Including the preterm human milk group along with the randomized formula groups, FPL acuity was correlated with the end-product ratio, 22:6ω-3/22:5ω-6 (r = -0.38, P < 0.01).

Gestational Age at Birth and Diet

The VEP and FPL acuity histograms for the full-term human milk groups tested at 57 and 66 wk postconception are shown in Figure 6. The logMAR full-term human milk group acuities were distributed normally (Kolmogorov-Smirnov P value range, 0.31–0.98), and the solid curves represent the best-fit normal distribution for each measure. These data provide a gold standard for optimal visual development in full-term infants.

The VEP and FPL acuity distributions for the full-term human milk group tested at 57 wk postconception (17 wk postnatal) and 66 wk postconception (26 wk postnatal) are shown as the thick and thin solid
Fig. 6. Visual evoked potential (VEP) and forced-choice preferential-looking (FPL) acuity of "gold standard" full-term groups at 57 and 66 wk post-conception. Bars represent the frequency distributions for each acuity measure. Solid curves represent the best-fit normal distributions. Acuity is expressed as log minimum angle of resolution (logMAR).

57 WEEKS

Fullterm Human Milk VEP Acuity

Fullterm Human Milk FPL Acuity

66 WEEKS

Fullterm Human Milk VEP Acuity

Fullterm Human Milk FPL Acuity

curves, respectively, in Figure 7. The full-term human milk group acuities (logMAR) were distributed normally (Kolmogorov-Smirnov $P$ value range, 0.32–0.98), and the solid curves represent the best-fit normal distribution for each measure. Also shown in Figure 7 are the frequency histograms of acuities obtained from the preterm human milk group tested at 57 wk postconception (26 wk postnatal). Overall, there was a significant effect of gestational age at birth on both VEP ($F = 9.85, P < 0.001$) and FPL acuities ($F = 18.40, P < 0.001$). Post hoc tests showed that the preterm human milk group acuities were significantly poorer than those of full-term human milk group infants when matched on the basis of postnatal age (26 wk, $P < 0.05$), but they did not differ significantly when matched on the basis of postconceptional age (57 wk).

The VEP and FPL acuity distributions for preterm human milk and full-term human milk group acuities (logMAR) were distributed normally (Kolmogorov-Smirnov $P$ value range, 0.31–0.98), and the solid curves represent the best-fit normal distribution for each measure. Also shown in Figure 8 are the frequency histograms of acuities obtained from the preterm corn oil group and the full-term formula group. Both of these groups received virtually no dietary $\omega$-3 fatty acids. For VEP acuity, there was a significant main effect of dietary group ($F = 11.55, P < 0.002$), but the effect of gestational age at birth and the interaction were not significant. For FPL acuity, there were significant main effects of dietary group ($F = 16.94, P < 0.001$) and gestational age at birth ($F = 5.63, P < 0.02$), but the interaction was not significant.

Discussion

Both VEP and FPL acuity development were influenced by the availability of $\omega$-3 fatty acids in the
Fig. 7. Visual evoked potential (VEP) and forced-choice preferential-looking (FPL) acuities of the preterm human milk group and the full-term human milk group. Thick solid curves represent the best-fit normal distributions obtained from the full-term human milk group at 57 wk post-conception (17 wk post-natal). Thin solid curves represent the best-fit normal distributions obtained from the full-term human milk group at 66 wk post-conception (26 wk post-natal). Bars represent the frequency distributions of the preterm human milk group at 57 wk post-conception (26 wk post-natal). Acuity is expressed as log minimum angle of resolution (logMAR).

The FPL acuity of the ω-3 fatty acid-deficient corn oil group was, on average, 0.12 log unit (0.40 octave) poorer than FPL acuity of the ω-3 LCPUFA-supplemented soy/marine oil group and 0.15 log unit (0.50 octave) poorer than FPL acuity of the preterm human milk group at 57 wk postconception. Similar differences were reported for control and ω-3 fatty acid deficient rhesus monkeys tested with FPL at a comparable stage of maturation (0.14 log unit [0.47 octave] at 4 wk postterm) and for a mixed population of healthy and ill preterm human infants tested with the informal “acuity card procedure” (0.08 log unit [0.27 octave] at 4 mo postterm). Our FPL acuity data also confirm the finding in rhesus monkeys that the ω-3 fatty acid-deficient group had poorer FPL acuity than published normative data for healthy full-term infants; the control group had FPL acuities comparable to the normative data. By contrast, data obtained with the informal acuity card procedure showed acuity development comparable to the normative data in the ω-3-deficient group and above-average acuities in the ω-3-supplemented group. This discrepancy may be related to differences between the FPL and acuity card procedures, to differences in inclusion and exclusion criteria for the preterm populations, or to the failure to gather full-term normative data at the site of the acuity card study.

Two gold standards of normal preterm visual development were used for comparison with the randomized formula-fed infants. The preterm human milk group was matched for gestational age at birth, birth weight, and postconceptional age at testing with the randomized groups, but these infants received at least 75% of their daily nutrition from human milk. The intrauterine group was matched with the randomized groups for postconceptional age at testing but received placental nutrition until 2-5 days before testing. By comparison, the corn oil group had significantly poorer VEP and FPL acuities, the soy oil group had poorer VEP acuity than the human milk group at 36 wk but not at other ages, and the soy/marine oil group had comparable acuities. These results suggest that only the provision of preformed ω-3 LCPUFAs in the diet allows for “normal” VEP and FPL acuity development over the range of ages studied. However, this conclusion must remain tentative because these two so-called gold standard groups were not randomized and it is possible that other nondietary differences between groups contributed to the pattern of results we observed.

The acuities of preterm infants tested at 57 wk postconception agreed well with the acuities of full-term infants in the soy/marine oil group received sufficient levels of ω-3 fatty acids, including preformed ω-3 LCPUFAs, to match the levels available from third-trimester intrauterine supply and from preterm human milk. This group consistently had higher ω-3 levels in erythrocyte membranes and VEP and FPL acuities than infants in the corn oil group, who received virtually no dietary ω-3 fatty acids. Preterm infants in the soy oil group received parent ω-3 fatty acid but no preformed ω-3 LCPUFAs. This group had intermediate ω-3 LCPUFA levels in erythrocyte membranes and showed significantly poorer VEP acuity at 57 wk compared with the soy/marine oil group. Taken together, these data suggest that dietary ω-3 LCPUFAs play an important role in the developing eye and brain of the preterm infant.
infants tested at 57 wk postconception, although the preterm infants had 9 additional weeks of visual experience. Both FPL and VEP acuity data from preterm and full-term infants fed human milk were consistent with the hypothesis that postconceptional age (physical maturation) is the major determinant of VEP and FPL acuity development rather than postnatal age (number of weeks of visual experience). The FPL results were consistent with other studies that found either no acceleration or only a very modest acceleration of FPL acuity development in preterm versus full-term populations recruited without regard to diet. However, a previous study of VEP acuity development suggested that preterm birth may accelerate acuity development. This apparent acceleration of preterm VEP acuity development may be caused, in part, by differences in feeding practices for the preterm versus full-term populations studied and/or the unique eligibility criteria for preterm infants used in the VEP studies.

Similar effects of diet on VEP and FPL acuity development were found among preterm and full-term populations at 57 wk postconception. In both groups, infants fed formula containing little or no ω-3 EFAs had poorer acuities than those receiving human milk. Because the human milk groups were not randomized, it is possible that other nondietary factors played a role in the acuity differences between human milk-fed and formula-fed groups. In addition, it is possible that other, as yet uninvestigated, differences in nutrients present in human milk versus infant formula may play a role in visual development. Nonetheless, these data offer the first evidence that the visual development of healthy full-term infants may be vulnerable to the effects of ω-3 fatty acid deficiency. There is some evidence to suggest that formula-fed full-term infants also may be at higher risk than human milk-fed infants for learning disability, poorer pattern recognition, and lower scores on picture intelligence, word reading, sentence completion, nonverbal abil-
ity, and mathematic-attainment tests administered at 8 yr and 15 yr of age.48

Taken together, our results suggest that dietary ω-3 fatty acids play an important role in visual development of the preterm infant. Current recommendations for preterm infant formula suggest minimum levels of linoleic acid49 and/or α-linolenic acid,50 but there is no upper limit proposed for linoleic acid. Most preterm formulas contain more linoleic acid than does human milk. No recommendations currently specify LCPUFA content of preterm infant formulas, and no commercially available formulas contain preformed LCPUFAs. Two factors may limit the ability of preterm infants to elongate and desaturate the parent EFAs to form LCPUFAs. First, high linoleic acid content may limit the formulation of ω-3 LCPUFAs in neural membranes and blood lipids because Δ6-desaturase is shared by both the ω-6 and ω-3 series.2,3,29,35-53 Second, there is evidence that desaturation of α-linolenic to DHA may be slow and inefficient in the preterm infant; either the enzyme is not fully active or the uptake of LCPUFAs by tissues exceeds the capacity of the neonatal liver to synthesize them.25,54 By contrast with commercially available preterm formula, the soy/marine oil formula and preterm human milk provide sufficient EFAs to match the intrauterine accretion rates of both ω-6 and ω-3 EFAs. They also provide preformed LCPUFAs, including DHA. Our results, considered in light of the preterm infant’s limited ability to elongate and desaturate parent EFAs, support the hypothesis that optimal visual development in the preterm infant may depend on a dietary source of ω-3 EFAs, including preformed ω-3 LCPUFAs, and a dietary ω-3:ω-6 fatty acid ratio similar to that found in preterm human milk.

Key words: preterm infants, acuity, visual development, docosahexaenoic acid, dietary fatty acids

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References