HK J Paediatr (new series) 1999;**4**:82-88

Feature Article

The Role of Long Chain Polyunsaturated Fatty Acids in Infant Nutrition

WJ GOLDMAN

Introduction

Long chain polyunsaturated fatty acids (PUFAs) are important to all living organisms because they are essential components of cell membranes. The necessity for the presence of these essential components of fats has been known at least since 1929.[1] Studies have been conducted which have demonstrated that the essential components of the human diet are linoleic acid [2] and linolenic acid. [3] Recent evidence has shown the importance of the PUFAs arachidonic acid (AA) and docosahexanoic acid (DHA) in infant cognitive and visual development.[4,5] The PUFAs AA and DHA are synthetic products derived from linoleic and linolenic acid metabolism.

Classification

Structurally, fatty acids are a linear chain of carbon atoms with a carbon tail at one end and an acid moiety at the other end. Double bonds may or may not be present.

Figure 1

Further classifications are made into families depending upon the locations of the double bond closest to the carbon tail. An omega-6 fatty acid has a double bond in the 6th position from the carbon tail and an omega 3 fatty acid is in the 3rd position from the carbon tail. Figure 2 contains some examples of fatty acids classified according to the relative position of the first double bond from the carbon tail.

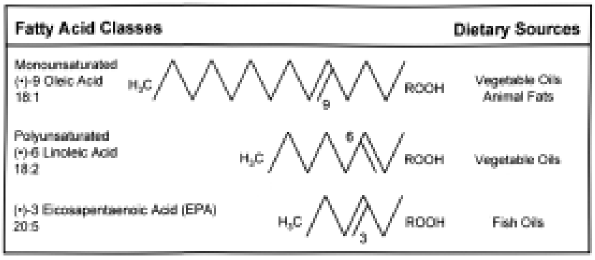


Figure 2

Table 1 contains a listing of some important PUFAs with their usual abbreviation and chemical shorthand. Thus Linoleic acid is abbreviated LA and the shorthand nomenclature 18:2ϖ-6 represents an 18-carbon chain with two double bonds, the first double bond occurring after the 6th carbon. 18:3ϖ-3 represents an 18 carbon chain with three double bonds, the first double bond occurring after the 3rd carbon.

Table 1

Name	Abbreviation	Shorthand
Linoleic Acid	LA	18:2 ϖ-6
γ-Linolenic Acid	GLA	18:3 ϖ-6
α-Linolenic Acid	LNA	18:3 ϖ-3
Arachidonic Acid	AA or ARA	20:4 ϖ-6
Eicosapentaenoic Acid	EPA	20:5 ϖ-3
Docosahexaenoic Acid	DHA	22:6 ϖ-3

Synthesis

The two main long chain polyunsaturated fatty acids which are relied upon for brain cell structure are DHA, an omega-3 fatty acid and AA, an omega-6 fatty acid. The

Medical & Regulatory Affairs, Wyeth Nutritionals International, St. Davids, PA, USA

WJ GOLDMAN *MD, Ph.D*

Correspondence to: WJ GOLDMAN

Received April 25, 1999

parent compounds, which synthesize these two fatty acids in the body, are α-linolenic acid and linoleic acid. Infants are likely to need DHA and AA in their diets, as they may be unable to synthesize sufficient amounts from α-linolenic and linoleic acid until 4 to 6 months postpartum.[6] Figure 3 represents a diagram of the LCPUFA synthetic pathway.

The omega-3 fatty acid series including linolenic acid, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are present as a major component of tissues Docosahexanoic acid is present as a major component of membrane phospholipids in retinal photoreceptors, cerebral gray matter and sperm. Linoleic acid an omega 6 fatty acid is a minor component of most membrane phospholipids while arachidonic acid is present in much higher concentrations. Oleic acid and eicosatrienoic acid, omega 9 fatty acids are components of many tissues including white matter and myelin (Table 2).

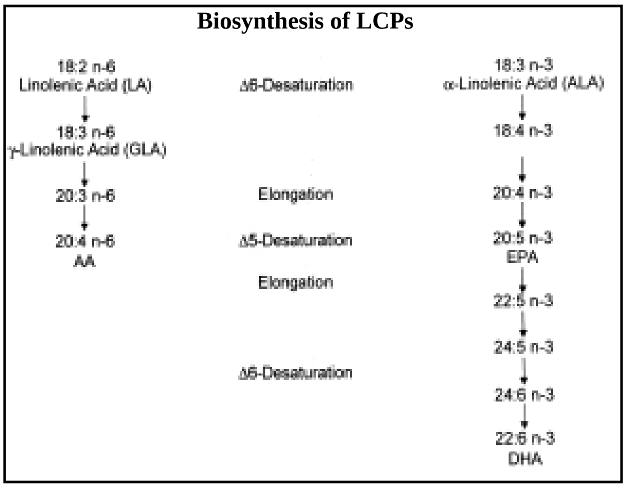


Figure 3

Deficiency Patterns

Characteristics of omega 3 and omega 6 deficiencies have been determined. The clinical features of an omega 3 deficiency include reduced learning and an abnormal ERG (retinal response to light) as well as impaired vision in the face of normal skin integrity but with fluid retention and normal growth. On the other hand, an omega 6 fatty acid deficiency results in growth retardation, skin lesions, reproduction failure, the occurrence of a fatty liver and fluid retention.[7] For infants, deficiencies in the amounts of DHA and AA and their metabolites in the diet during infancy may affect the maturation of the central nervous system, including visual development and intelligence.[8]

The relationship between DHA and AA in terms of their effects upon growth has been well established. Carlson[9] found that preterm infants fed with EPA and DHA as the sole LCPUFA component of the diet exhibited growth retardation, which corresponded to a progressive deficiency of AA. It was soon discovered that supplementation with AA in addition to DHA is essential for proper growth and development. Several investigators[10,11] have shown that only a balanced addition of DHA and AA supports optimal tissue accretion of both of these important fatty acids.

A growth study conducted by Vanderhoff[12] and colleagues in preterm infants showed that there were no significant differences in weight, length and head circumference as a result of receiving a formula containing

Table 2 Metabolic Pathways for the Synthesis of Various Essential Fatty Acids and Their Tissue Distribution

Fatty Acid Series	Major Members	Tissue Distribution
n3	Linolenic Acid (18:3n3)	Minor Component of Tissues
	Eicosapentaenoic Acid (20:5n3)	Minor Component of Tissues
	Docosahexaenoic Acid (22:6n3)	Major Component of Membrane Phospholipids in Retinal Photoreceptors, Cerebral Gray Matter, and Sperm
n6	Linoleic Acid (18:2n6)	Minor Component of Most Tissues
	Arachidonic Acid (20:4n6)	Major Component of Most Membrane Phospholipids
	Docosapentaenoic Acid (22:5n6)	Very Low in Normal Tissues but Replaces 22: 6n3 in n3 Fatty Acid Deficiency
n9	Oleic Acid (18:1n9)	Major Component of Many Tissues, Including White Matter and Myelin
	Eicosatrienoic Acid (20:3n9)	Accumulates in Total Essential Fatty Acid Deficency

From Neuringer M. Connor WE: n-3 Fatty Acids in the Brain and Retina: Evidence for Their Essentiality Nutr Rev 1986; 44: 285-294

LCPUFAs as compared to preterm infants receiving human milk or a formula without supplementation from birth to 40 weeks postconceptional age (Table 3). The finding further suggests that feeding a diet balanced in both DHA and AA is equivalent in terms of growth, safety and tolerance to preterm infants receiving the two formulas or human milk.

Tissue Distribution

Breast Milk

Koletzko et al [13] have reviewed a number of studies of the PUFA content of breast milk. In their report they have reviewed 14 European studies and 10 African studies which have measured the fatty acid content in addition to the PUFA content of breast milk. While individual levels of fatty acids may vary from community to community in accordance with the mother's diet as can be seen in Table 4, the DHA to AA ratio remains at a relatively constant value of 1.6 to 2.2.

Serum Levels

Serum levels of the long chain polyunsaturated fatty acids DHA and AA in term infants have been determined by Gibson et al. [14] He and his colleagues studied the effects

Table 3 Growth Study at 40 Wks Postconceptional Age (Mean ±)

	Human Milk (n = 65)	**Control[a] (n = 66)**	**LCPs[b] (n = 60)**
Weight (g)	2892.9	3270.7	3376.2
	±492.38	±569.83	±436.53
Length (cm)	48.55	49.01	49.95
	±2.65	±2.61	±2.77
Head Circumference (cm)	34.79	35.33	35.62
	±1.49	±1.47	±1.3

[a] 24 Kcal/oz Preterm Formula; [b] Preterm Formula Supplemented with ARA (0.6%) and DHA (0.4%). Vanderhoff et al., 1997

Table 4 Medians and Ranges Calculated from Average Fatty Acid Values Reported in the Reviewed Studies on Mature Human Milk in Europe and Africa

	Europe (14 Studies)	**Africa (10 Studies)**
Fatty Acid Totals (% wt/wt)		
Saturated	45.2 (39.0 - 51.3)	53.5 (35.5 - 62.3)
Monosaturated	38.8 (34.2 - 44.9)	28.2 (22.8 - 49.0)
n-6 + n-3 PUFA	13.6 (8.5 - 19.6)	16.6 (6.3 -24.7)
n-6 PUFA (% wt/wt)		
C18:2n-6 (Linoleic Acid)	11.0 (6.9 - 16.4)	12.0 (5.7 - 17.2)
C 20:2n-6	0.3 (0.2 - 0.5)	0.3 (0.3 - 0.8)
C 20:3n-6	0.3 (0.2 - 0.7)	0.4 (0.2 - 0.5)
C 20:4n-6 (Arachidonic Acid)	0.5 (0.2 - 1.2)	0.6 (0.3 - 1.0)
C 22:4n-6	0.1 (0.1 - 0.2)	0.1 (0.0 - 0.1)
C 22:5n-6 (Docosapentaenoic Acid)	0.1 (0.0 - 0.2)	0.1 (0.1 - 0.3)
Total n-6 LCP	1.2 (0.4 - 2.2)	1.5 (0.9 - 2.0)
n-3 PUFA (% wt/wt)		
C 18:3n-3 (Linolenic Acid)	0.9 (0.7 - 1.3)	0.8 (0.1 - 1.44)
C 20:5n-3 (Eicosapentaenoic Acid)	0.2 (0.0 - 0.6)	0.1 (0.1 - 0.5)
C 22:5n-3	0.2 (0.1 - 0.5)	0.2 (0.1 - 0.4)
C 22:6n-3 (Docosahexaenoic Acid)	0.3 (0.1 - 0.6)	0.3 (0.1 - 0.9)
Total n-3 LCP	0.6 (0.3 - 1.8)	0.6 (0.3 - 2.9)
Ratios		
18:2n-6/18:3n-3	12.1 (8.6 - 16.9)	14.2 (8.8 - 157)
20:4n-6/22:6n-3	1.8 (0.7 - 5.0)	2.2 (0.7 - 10)
n-6 LCP/n-3 LCP	2.7 (0.3 - 3.7)	2.4 (0.8 - 6)
Polyunsaturated/Saturated	0.3 (0.2 - 0.5)	0.3 (0.1 - 0.5)
Monounsaturated/Saturated	0.9 (0.7 - 1.1)	0.5 (0.4 - 1.4)

Koletzko B. et al. The Fatty Acid Composition of Human Milk in Europe and Africa. The Journal of Pediatrics 120:562-70 April 1992 of varying the dietary intake of DHA and AA in term infants upon serum levels of LCPUFAs (Table 5). In their study five different levels of intake were assessed. One group received a standard diet with low levels of LCPUFAs; a second group received human breast milk; another group received a diet containing 0.2% AA and 0.2% DHA; a fourth group received 0.32% AA and 0.2% DHA; the fifth group received 0.4% AA and 0.25% DHA. An analysis of the plasma phospholipids was conducted both at 0 and 6 weeks of study. At 6 weeks, the plasma phospholipids which resulted from feeding the blend containing 0.32% AA with 0.2% DHA and the blend containing 0.4% AA with 0.25% DHA were noted to approach plasma phospholipid levels which resulted from feeding human milk.

Similar results have been reported to occur in preterm infants [15,16] and in term infants. [17,18] In fact, in the preterm infant study by Gross et al.,[15] it was demonstrated that the addition of AA (0.6%) and DHA (0.4%) to a preterm formula maintained a phospholipid profile in preterm infants that was closer to the serum phospholipid level of preterm infants fed human milk.

Brain Levels

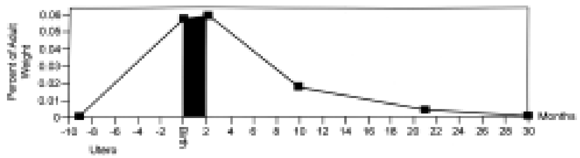
It is generally agreed that the majority of brain growth occurs in-utero. However, a term infant's brain development is still not complete at the time of birth. A substantial and very high rate of brain growth occurs during the first three months of life. Figure 4 demonstrates that an additional finite level of brain growth will occur during this time and the availability of appropriate nutrients is critical for neutral development.[19]

Clandinin, et al., [20] have evaluated the fatty acid accretion rates in infant brains. These investigators found that postpartum deposition of fatty acids lagged for the first four weeks of life but increased more dramatically during the latter stages of infancy. The greatest deposition of fatty acids was noted by these investigators in previous studies to occur in the third trimester of pregnancy. It has been previously noted that infants may be unable to synthesize fatty acids with higher degrees of unsaturation or elongation until four to six months postpartum. [6] There is a suggestion that during this period of time the preformed DHA and AA necessary for CNS accretion are similarly not available if the infant receives a formula which is not supplemented with PUFAs. Farquharson[21] and his colleagues have stated that as the phospholipids are known to perform an important role in membrane function and are possibly integral to neurotransmission, it is recommended that breast milk substitute infant formulas should contain n-3 and n-6 series polyunsaturated fatty acids in proportions similar to those of human milk.

Visual Acuity

Since brain and retinal tissue long chain fatty acid content and accretion is exceptionally high in the infant, it is suggested that visual acuity might be expected to be influenced by the fatty acid content of the diet. A study conducted by Uauy and his colleagues[22] evaluated electroretinographic responses in a group of infants fed formulas containing various levels of omega-3 and omega-6 fatty acids starting at 36 weeks postconceptual age. One group received an unsupplemented formula sufficient in linoleic acid but relatively deficient in α-linolenic acid,

Brain Growth



Adapted from: Dobbing J., (1974). In: Scientific Foundation of Pediatrics, p.565 Eds: J.A. Davies and J. Dobbing. Heinemann, London

Figure 4

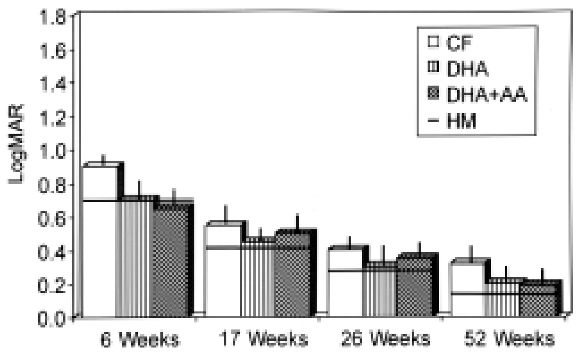
Table 5 Plasma Phospholipids ARA & DHA Levels [μg/ml; $\bar{x}$ (S.D.)]

		Control	Blend 1	Blend 2	Blend 3	HM
ARA						
Week	0	156 (26)[a]	153 (32)[a]	143 (33)[a]	146 (37)[a]	183 (30)[b]
	6	95 (16)[a]	119 (17)[a,b]	134 (47)[b]	139 (23)[b]	148 (27)[c]
DHA						
Week	0	50 (11)[a,b]	47 (12)[a,b]	45 (15)[a]	45 (13)[a]	57 (16)[b]
	6	28 (6)[a]	50 (6)[b]	52 (16)[b]	54 (10)[b]	55 (13)[b]

Different Superscripts Above Indicate P<0.05. Plasma Triglyceride, Plasma Cholesterol Ester and Erythrocyte Phospholipid ARA and DHA Levels Showed Similar Results. Gibson et al., 1997 another was fed breast milk, a third group received α-linolenic acid supplementation while a fourth group received a combination of α-linolenis acid and marine oil which contained eicosapentaenoic acid and docosahexaenoic acid. As is demonstrated by Table 6, the EPA/DHA supplemented formula resulted in an electroretinographic response that was similar to the response of infants receiving breast milk. An additional supply of long-chain omega-3 fatty acid is necessary to enhance and sustain rod electroretinographic function.

In a confirmatory study conducted by Birch, et al., [23] visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants was established. These investigators divided four groups of infants into those receiving a control formula, one receiving a formula supplemented with DHA, another receiving a formula supplemented with both DHA and AA and the fourth group receiving breast feedings. Outcomes measured included sweep VEP and FPL acuities expressed as the Log of the Minimum Angle of Resolution (LogMAR) at enrollment, 6,17, 26 and 52 weeks. 20/20 vision corresponds to a minimum angle of resolution of 1 min arc and a LogMAR of 0.0. 20/200 vision corresponds to a minimum angle of resolution of 10 min arc a LogMAR of 1.0. Figure 5 demonstrates that sweep VEP is a function of diet during the first year of life. One can see that DHA/AA or DHA supplementation in terms of sweep VEP results in visual acuity which is very similar to the results found to occur in breast-fed infants. Visual acuity in the control formula group was significantly poorer than in the other groups. It was noted by these authors that FPL acuity (Figure 6) is less sensitive to subtle differences in visual acuity than the sweep VEP.

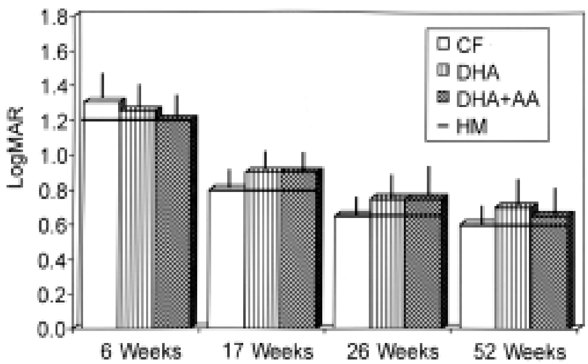
Sweep VEP Acuity



Sweep VEP Acuity as a Function of Diet Group During the First Year of Life: Control Formula (□), DHA-Supplemented Formula (▥), DHA + AA Supplemented Formula (▩), Human Milk (—). The Control Formula Group Had Significantly Poorer Acuity than the Other Groups at 6, 17, and 52 Wk (See Table 7 for Details). (|) Indicate the Standard Deviations.

Figure 5

FPL Acuity



FPL Acuity as a Function of Diet Group During the First Year of Life: Control Formula (□), DHA-Supplemented Formula (▥), DHA + AA Supplemented Formula (▩), Human Milk (—). (|) Indicate the Standard Deviations. No Significant Differences Were Found Among Diet Groups.

Figure 6

Table 6 Electroretinographic Responses At 36 WK Postconceptual Age (MEAN ± SD)*

	Human Milk (n = 10)	Unsupplemental Formula (n = 10)	LNA Supplemental Formula (n = 10)	EPA/DHA Supplemental Formula (n = 10)	ANOVA F	ANOVA P
Rod Function						
Log Threshold (scot td-s)	0.414 ± 0.59[a]	1.105 ± 0.37[b]	0.739 ± 0.64[a,b]	0.410 ± 0.63[a]	3.309	<0.028
Log V_{max} (μV)	1.20 ± 0.14[a]	1.02 ± 0.05[b]	1.07 ± 0.13[a,b]	1.20 ± 0.17[a]	4.99	<0.005
Log K (scot td-s)	1.25 ± 0.54	1.72 ± 0.31	1.43 ± 0.6	1.25 ± 0.55	1.94	<0.14
Cone Function						
Log Threshold (phot td-s)	-0.11 ± 0.24	0.09 ± 0.15	-0.04 ± 0.03	-0.04 ± 0.24	NS	NS
CFF (Hz)	51.5 ± 6.6	48.5 ± 5.6	48.9 ± 6.3	47.4 ± 6.9	NS	NS

*Groups with Different Superscripts are Significantly Different (p<0.05) Using Newman-Keuls Multiple Comparison Test. Scot td-s, Scotopic Troland-Seconds; Phot td-s, Photopis Troland-Seconds

Uauy et al. Ped Res 1990; 28: 485-492

Cognitive Function

In 1992 Lucas and his colleagues[24] reported in the Lancet the results of a study that they undertook wherein they had examined the IQ of 7 1/2 to 8 year old children who were either formula fed or breast fed as infants. Even after accounting for multiple variables, such as mother's education and social class, there was an 8.3 advantage for the breast fed group (Table 7). It was suggested that the presence of long chain polyunsaturated fatty acids in breast milk which was not present in formula milks accounted for the relative advantage of breast feeding in terms of IQ.

A further demonstration of the beneficial effects on cognitive function as a consequence of feeding LCPUFAs to infants can be provided by the study reported by Willets et al.[25] Willets and colleagues undertook this study to determine whether feeding LCPUFAs in infancy made any difference in cognitive function in later life. Ninety-three infants were recruited into the study. Seventy-two infants were randomized to receive either a formula supplemented with LCPUFAs (n = 34) or and unsupplemented formula (n = 38) from birth to age 4 months. Problem solving was assessed at 10 months of age. Twenty-one of the supplemented group and twenty-three of the unsupplemented group completed the problem solving assessment. Infants were required to solve a three step problem which included a barrier, cloth or cover removal to retrieve a toy (Table 8).

Table 9 lists the result obtained by the 10 month old infants separated according to diet. The study showed that

Table 7 IQ At 7 1/2-8 Years

	Mean (SEM) Scores		
	Formula Fed	**Breast Fed**	**Advantage for Breast Fed Babies (95%CI)**
Abbreviated WISC-R			
Verbal Scale	92-0 (2-0)	102-1 (1-3)	10-1 (4-7, 15-5)*
Performance Scale	93-2 (1-7)	103-3 (1-2)	10-2 (6-0, 14-2)*
Overall IQ	92-8 (1-6)	103-0 (1-2)	10-2 (6-3, 14-1)*

* p<0.001, Group I vs. Group II; CI= Confidence Interval. Lucas Lancet 339: 264-269, 1992 et al

Table 8 Criteria for Scoring Intention on Steps of Three-Step Problem

Step	No Intention (0)	Possible Intention (1)	Clear Intention (2)
Barrier			
Barrier Behaviour	Play: Barrier Not Removed	Hesitant Removal	Remove Barrier
Fixation	Fixate Away from Cloth	Fixate Briefly Away from Cloth	Fixate Cloth Continuously
Cloth Retrieval	Ignore Cloth	Attempt to Grasp Cloth	Pick Up Cloth
Cloth			
Cloth Behaviour	Play: Cover Not within Reach	Heistant Pulling	Pull Cloth
Fixation	Fixate Away from Cover	Fixate Briefly Away from Cover	Fixate Cover Continuously
Cover Retrieval	Ignore Coveer	Attempt to Grasp Cover	Pick Up Cover
Cover			
Cover Behaviour	Play: Cover Not Removed	Hesitant Removal	Remove Cover
Fixation	Fixate Away from Toy	Fixate Briefly Away from Toy	Fixate Toy Continuously
Toy Retrieval	Ignore Toy	Attempt to Grasp Toy	Pick Up Cover

Source: The Lancet, Vol. 352, August 29, 1998

Table 9 Median (Quartiles) Problem-Solving Scores on Entire Problem and Each Individual Step

Step	LCPUFA (n = 21)	No-LCPUFA (n = 23)	p
Intention Score			
Entire Problem	14.0 (11.8, 17.1)	11.5 (10.0, 13.3)	0.035
Barrier Step	5.5 (4.3, 6.0)	4.8 (3.5, 5.8)	0.221
Cloth Step	5.0 (4.5, 6.0)	4.5 (3.5, 5.8)	0.147
Cover Step	4.3 (2.6, 5.3)	2.5 (1.0, 3.5)	0.032
Intentional Solutions			
Entire Problem	2.0 (0.5, 3.0)	0.0 (0.0, 0.2)	0.021
Barrier Step	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.337
Cloth Step	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)	0.234
Cover Step	3.0 (1.5, 3.5)	1.0 (0.0, 2.0)	0.005

Source: The Lancet, Vol. 352, August 29, 1998 infants with LCPUFA supplementation had significantly improved results than the infants who received a diet without LCPUFAs. These authors suggested that formula fed term infants may benefit from LCPUFA supplementation and the effects persist beyond the period of supplementation. They further suggest that LCPUFAs may be important for the development of childhood intelligence.

Conclusion

The long chain polyunsaturated fatty acids DHA and AA are found in infants brains, eyes and serum. Long chain polyunsaturated fatty acids are also found in breast milk. Infants have a limited capacity to synthesize long chain polyunsaturated fatty acids which are necessary for proper neurological development and visual acuity. Infants who are not breast fed must be given a formula that contains long chain polyunsaturated fatty acids.

References

1. Burr GO, Burr MM. A new deficiency disease produced by rigid exclusion of fat from the diet. J Biol Chem 1929; 82: 345-67.
2. Hansen AE, Haggard ME, Boelshe AN, Adams DD, Wiese HF. Essential fatty acids in infant nutrition, III: clinical manifestations of linoleic acid deficiency. J Nutr 1958; 66: 565-72.
3. Holman RT, Johnson SB, Hatch TF. A case of human linolenic acid deficiency involving neurological abnormalities. Am J Clin Nutr 1982; 35: 617-23.
4. Agostoni C, Trojan S, Bello R, Riva E, Giovannini M. Neurodevelopmental quotient of healthy infants at 4 months and feeding practice: the role of long-chain polyunsaturated fatty acids. Pediatr Res 1995; 38: 262-6.
5. Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. Pedriat Res 1998; 44: 201-9.
6. Makrides M, Neumann MA, Simmer K, Gibson RA. Erythrocyte fatty acids of term infants fed either breast milk, standard formula, or formula supplemented with long-chain polyunsaturates. Lipids 1995; 30: 941-8.
7. Neuringer M, Connor WE. n-3 fatty acids in the brain and retina: evidence for their essentially. Nutr Rev 1986; 44: 285-94.
8. Hardy SC, Kleinman RE. Fat and cholesterol in the diet of infants and young children: implications for growth, development, and long-term health. J Pediatr 1994; 125: S69-S77.
9. Carlson SE, Cooke RJ, Werkmann SH, Trolley EA. First year growth of preterm infants fed standard compared to marine oil n-3 supplemented formula. Lipids 1992; 27: 901-7.
10. Carlson SE, Werkmann SJ, Peeples JM, Cooke RJ. Arachidonic acid status correlates with first year growth in preterm infants. Proc Natl Acad Sci 1993; 90: 1073-7.
11. Clandinin MT, Van Aerde J, Field DJ, Parrott A, Flores L, Lien E. Preterm infant formulas: effects of increasing levels 20:4 (6) and 22:6(3) on the fatty acid composition of plasma and erythrocyte phospholipids. J Pediatr Gastroenterol Nutr 1996; 22: 432.
12. Vanderhoff J, Gross S, Hegyi T, et al. A new arachidonic acid (ARA) and docosahexanoic acid (DHA) supplemented preterm formula: growth and safety assessment. Pediatr Res 1997; 41: 4.
13. Koletzko B, Thiel I, Abiodun PO. The fatty acid composition of human milk in Europe and Africa. J Pediatr 1992; 120: S62-S70.
14. Gibson R, Makrides M, Neumann M, Pramuk K, Lien E, Euler A. A dose response study of arachidonic acid in formulas containing docosahexaenoic acid in term infants. Prost Leuko Essen Fatty Acids 1997; 57:198.
15. Gross S, Vanderhoof J, Hegyi T, et al. A new arachidonic acid (ARA) and docosahexanoic acid (DHA) supplemented preterm formula: effect on plasma and erythrocyte phospholipid fatty acids. Pediatr Res 1997; 41: 232A.
16. Koletzko B, Schmidt E, Bremer HJ, Hang M, Harzer G. Effects of dietary long-chain polyunsaturated fatty acids on the essential fatty acid status of premature infants. Eur J Pediatr 1989; 148: 669-75.
17. Makrides M, Neumann MA, Simmer K, Gibson R. Erythrocyte fatty acids of term infants fed either breast milk, standard formula, or formula supplemented with long-chain polyunsaturates. Lipids 1995; 30: 941-8.
18. Koletzko B, Decsi T, Demmelmair M. Arachidonic acid supply and metabolism in human infants born at full term. Lipids 1996; 31: 79-83.
19. Dobbing J. In: Davies JA, Dobbing J, editors. Scientific Foundations of Pediatrics. London: Heinemann 1974, p565.
20. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. Early Human Develop 1980; 4: 131-8.
21. Farquharson J, Jamieson EC, Abbasi KA, Patrick WJ, Logan RW, Cockburn F. Effect of diet on the fatty acid composition of the major phospholipids of infant cerebral cortex. Arch Dis Child 1995; 72: 198-203.
22. Uauy RD, Birch DG, Birch EE, Tyson JE, Hoffman DR. Effect of dietary omega-3 fatty acids on retinal function of very-low-birth-weight neonates. Pediatr Res 1990; 28: 485-92.
23. Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. Pediatr Res 1998; 44: 201-9.
24. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. Lancet 1992; 339: 261-4.
25. Willatts P, Forsyth JS, DiModugno MK, Varma S, Colvin M. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. Lancet 1998; 352:688-91.