Nutrients and neurodevelopment: Lipids. Update

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ABSTRACT

Nutrients, lipids in particular, make up the central nervous system structure and play major functional roles: they stimulate development, migration, and nerve cell differentiation. They are part of gray matter, white matter, nerve nuclei, and synaptogenesis.

Breast milk contains lipids which are crucial for infant brain development. The lipid profile of breast milk was used as a guideline for the development of breast milk substitutes. However, to date, no substitute has matched it. Complementary feeding should include docosahexaenoic acid, arachidonic acid, other polyunsaturated fatty acids, saturated fatty acids, and complex lipids found in milk fat.

The lipid composition of breast milk depends on maternal intake and nutritional status during pregnancy and breast-feeding. It has a great impact on development.

Our goal is to review scientific literature regarding the role of lipids on infant brain development and the importance of breast milk lipid composition, maternal diet, and complementary feeding.

***Key words**: infant development, central nervous system, nutrition, breast milk, lipids.*

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INTRODUCTION

Cognitive development during childhood is a complex process influenced by multiple genetic and environmental factors interacting with one another. Establishing the role of nutrients, in isolation from many covariates and confounding factors, is a challenging task.

During gestation, at 18 days of embryonic development, the neural plate is formed, which then turns into a neural groove that converts into a tube that closes completely at 28 days. Between weeks 8 and 18 of gestation, up to 200 000 neurons are formed per minute and, by one year of age, glial cells –responsible for myelination– reach their highest production level.[1-3] During development, nerve cells become arborized and stratified into a laminar pattern. They connect with one another and form up to 200 billion synapses. They make up networks for sensory processes, visual and auditory impressions, which may even be detected at birth. This means that, at this stage of development, the rudiments of neuronal groups are provided, which consist of the self-referential area, autobiographical memory, and consciousness. These areas expand during development to allow communication with the outer world and form what will become an individual's social networks.[4] Nutrition, particularly lipids, play a major role in brain development, which reaches 80% of its adult size by two years of age.

Breast milk is made up of essential lipids, such as saturated fatty acids (SFAs), long-chain omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), cholesterol, and complex lipids.[5,6]

Breast-feeding is considered to be the best option for infant feeding; and for this reason it should be promoted, protected, and supported as the only nutritional source for infants.

The lipid composition of breast milk depends on maternal intake and nutritional status.[7,8] Therefore, as of the time of conception, maternal nutritional status is an important determining factor of fetal development and growth.[9]

If feeding should be supplemented or replaced with a breast milk substitute, it is necessary to make sure that its nutritional composition is adequate. The composition of other complementary foods should also be controlled and warranted, and fatty acid levels in such foods should be identified, given that recommendations have changed over the past few years.[10]

The goal of this study is to review scientific literature regarding the role of lipids on infant brain structure and function, and provide pediatricians with knowledge on the importance of maternal diet, breast milk lipid composition, and complementary feeding.

METHODOLOGY

Information was updated after reviewing the following databases: MEDLINE, through PubMed, TRIP Database, and LILACS.

The search strategy included the following terms: lipids, dietary fat, infant development, central nervous system, visual maturation, breast milk, breast-feeding, complementary feeding, maternal nutrition, nursing mothers, pregnancy, saturated fatty acids, polyunsaturated fatty acids, docosahexaenoic acid (DHA), arachidonic acid (ARA), complex lipids, cholesterol.

Lipids

Lipids are a heterogeneous group of organic substances that share the fact that they are non-polar molecules, insoluble in water, and soluble in organic solvents, and are formed by carbon, hydrogen, oxygen, and sometimes, phosphor, nitrogen, and sulfur. Lipids are primarily triglycerides; i.e., three fatty acids esterified on a glycerol backbone, although there may also be two fatty acids bonded to a glycerol chain with a third carbon bonded to phosphoric acid, ethanolamine, choline, or inositol.

Breast milk and milk substitutes are made up of lipids which are crucial for infant brain development, including SFAs, monounsaturated fatty acids (MUFAs), PUFAs, cholesterol, and complex lipids.

Traditionally, lipids have been considered the source of energy in infants' dietary requirements; at present, it is also known that they play a major role in brain development. Approximately 50%-60% of brain dry weight is lipid content, long-chain PUFAs that are not available for energy metabolism.[4,11]

Fatty acids are the most relevant structures within lipids; they are part of phospholipids and glycolipids, the molecules that make up the lipid bilayer of all cell membranes.

Fatty acids

Fatty acids are divided into two groups based on their structural characteristics: SFA and unsaturated fatty acids (UFAs). Depending on the degree of unsaturation, UFAs may be further classified into MUFAs and PUFAs. While MUFAs have a single double bond, PUFAs have more than one. The more double bonds in a fatty acid, the higher the polyunsaturation, and depending on the position of the double bond –counting from the outermost carbon to the functional carboxylic group–, three series are formed: omega-9 (first bond located at the ninth carbon), omega-6 (first bond located at the sixth carbon), and omega-3 (first bond located at the third carbon).[12-14]

Omega-9 are not essential fatty acids because unsaturation may be introduced by the body into a SFA at the ninth carbon and thus they may be synthesized from a saturated fat. This is not the case with omega-6 and omega-3 fatty acids. Unsaturation cannot be introduced by our body into the omega-6 and -3 positions; therefore, there are two precursors: linolenic acid (C18:2n6), and α-linolenic acid (C18:3n3), which are essential and must be provided in the diet.[12-14] Diet should include these acids in adequately determined proportions; a poor or imbalanced intake causes serious metabolic alterations.

Saturated fatty acids

SFAs are not just a source of energy; they also play metabolic and structural roles. The first step in fatty acid biosynthesis is the synthesis of palmitic acid (hexadecanoic acid), a 16-carbon SFA; the other fatty acids are obtained through modifications of palmitic acid. The body may synthesize almost all fatty acids it requires from palmitic acid, through a combination of elongation, desaturation, and hydroxylation mechanisms taking place in the endoplasmic reticulum and the mitochondria. Thus, two carbon units are added to the palmitic acid 16-carbon chain, forming fatty acids of up to 24 carbons. But it cannot form a PUFA.[14] Essential fatty acids (EFAs) provided in the diet are necessary for this.[15]

The most common SFAs in infant nutrition have 12-, 14-, 16- and 18-carbon chains. Palmitic acid is an important component of breast milk; it accounts for approximately 25% of fatty acids in its composition, 60%-85% of which are located at the sn-2 position on triacylglycerol.[15,16]

Adding palm oil (high in palmitic acid) to breast milk substitutes allows the formulation to be more similar to breast milk lipid composition. However, one of the most critical aspects of formulations is nutrient bioavailability. Adding palm oil allows having more than 20% of palmitic acid, but only about 15% is located at the sn-2 position. Unlike breast milk, palmitic acid in vegetable oils is primarily located at the sn-1 and sn-3 positions.[16]

A study conducted in our setting on lipid composition of formula milk available in the market indicated that only breast milk substitutes containing milk fat or artificially structured lipids have more than 40% of palmitic acid at the sn-2 position. Palmitic acid is preferably absorbed bonded to glycerol at the sn-2 position, as monoacylglycerol.[17]

Besides playing a structural role in nervous tissue, palmitic acid has a specific function: it allows proteins to move in a fatty environment, such as the central nervous system. This process is called palmitoylation. The covalent attachment of a long-chain fatty acid (predominantly palmitate) onto a cysteine residue via a thioester bond is called S-palmitoylation.[18]

Across all studied vertebrate species, myelin proteolipid protein (PLP) contains approximately equal amounts of palmitic and stearic acids, among others.[18]

There is evidence that newly formed synapses may regulate the dynamic protein palmitoylation process in critical periods of early development, including a reduced palmitoylation of GAP-43, a specific axonal growth-associated protein present in growth cones.[19,20] This means that the process regulates very important functions. Thus, palmitic acid is involved in palmitoylation, gliogenesis, synaptogenesis, and myelination processes.

Polyunsaturated fatty acids

From fertilization, PUFAs are involved in neurogenesis, neuronal migration, gliogenesis, synaptogenesis, and myelination. The greater proportion of DHA is found in the membranes of synaptosomes and neuronal mitochondrias.[21-25]

Both DHA and ARA account for approximately 20% of brain fatty acid content and are involved in early neurodevelopment by promoting neural development, repair and myelination.[26,27]

DHA incorporates into brain phospholipids, especially phosphatidylcholines, phosphatidylethanolamines, and sphingolipids, as demonstrated in experimental animals. DHA deposits heavily in the sn-2 position of phospholipids, i.e., it esterifies the main hydroxyl in glycerol that is part of phospholipids. The sn-1 position is occupied by choline, ethanolamine, serine, or inositol, depending on the phospholipid. The sn-3 position is mostly occupied by a SFA, mainly palmitic acid.[15,17] ARA shares the sn-2 position in phospholipids with DHA, but it may also be minimally present at the sn-3 position, especially when sn-2 is occupied by DHA.[28-30]

Supplementation with DHA and ARA in pregnant women and nursing mothers has proven to improve infant visual acuity.[31] The same effect was demonstrated in term newborn infants who received complementary feeding with DHA supplementation.[32]

However, the impact of PUFA supplementation on cognitive development is controversial, both in term and preterm newborn infants. Several reviews have been done but failed to demonstrate positive effects of PUFA supplementation.[25,33,34]

Most clinical trials have established that cognitive assessment should be done at 18 months of age, although a significant part of cognitive abilities become apparent at a later stage. Recent publications that assessed cognitive development between 18 months and 6 years of age showed benefits in children who received PUFA supplementation during infancy compared to those who did not.[35,36]

Several publications recommend introducing ARA and DHA supplementation in pregnant women, nursing mothers, neonates, and infants. Pregnant women and nursing mothers should receive 200 mg/day of DHA.[21-25]

Breast-feeding is strongly recommended in the case of healthy infants because it provides long-chain PUFAs. If breast-feeding is not possible, current recommendations indicate using a breast milk substitute that provides adequate DHA levels (0.2%-0.5% of total fat), with at least an equivalent amount of ARA.[21]

Cholesterol

Cholesterol undergoes endogenous synthesis from dietary lipids of animal origin and mammalian milk. It is the substrate of bile acid, lipoprotein, vitamin D, and hormone synthesis. Cholesterol is responsible for stabilizing cell membrane structure and function through balance and interaction with DHA, among other purposes.[7]

Towards the end of pregnancy and in the first months of life, cholesterol is incorporated into the brain. A biochemical sequence has been described: the incorporation of lipid and myelin-associated specific proteins is followed by sphingomyelin and cerebrosides, among others.[37]

The high level of cholesterol in breast milk may be the reason why total and LDL (low-density lipoprotein) serum cholesterol levels are higher in nursing infants compared to those fed with breast milk substitutes.[7]

Complex lipids

These are non-saponifiable lipids whose molecular structure contains –in addition to carbon, hydrogen, and oxygen– nitrogen, phosphor, sulfur or a carbohydrate. These are the main molecules that make up the membrane lipid bilayer, so they are also called membrane lipids. They include phospholipids (phosphoglycerides and phosphosphingolipids) and glycolipids (cerebrosides and gangliosides). The most important phosphosphingolipid is sphingomyelin, the main component of the myelin sheath covering neuronal axons. Gangliosides play a major role in neuron synapsis and neurotransmission by facilitating the binding of transmitter molecules to synaptic membranes. They are also involved in neurogenesis, information storage, and the memory formation process. Brain development and maturation are associated with increasing ganglioside levels, a greater accretion in the cerebral cortex gray matter during the pre- and early post-natal periods.[7,37,38] The concentration of complex lipids is higher in the breast milk fat globule membrane.[39]

FINAL COMMENT

Neurodevelopment is a complex mechanism intertwined with genetic and epigenetic factors. There is a constant concern regarding the contribution of nutrition to development in general, and to neurodevelopment in particular. Knowledge of such contribution by the health team strengthens recommendations. The importance of a natural diet, breast milk and the act of offering it, breast-feeding, is paramount.

The decision to nurse has major consequences for the future cognitive development of children. Breast milk lipid profile was used as a guideline for those who developed breast milk substitutes. However, to date, no substitute has matched it. Maternal nutrition during pregnancy and breast-feeding is now becoming more important given the impact each nutrient may have on development. PUFA intake by nursing mothers has an impact on breast milk lipid composition.

Complementary feeding should include DHA, ARA, other PUFAs of vegetable origin, SFAs, such as palmitic acid at the sn-2 position (milk fat or structured lipids), and other complex lipids found in milk fat. ■

REFERENCES

1. Yamaguchi Y, Miura M. How to form and close the brain: insight into the mechanism of cranial neural tube closure in mammals. *Cell Mol Life Sci* 2013;70(17):3171-86.
2. Sadler TW. Langman Embriología Médica. 12.a ed. Philadelphia: Lippincott Williams & Wilkins; Sistema nervioso central. 2012.Capítulo 18:287-320.
3. Wozniak JR, Lim KO. Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neurosci Biobehav Rev* 2006;30(6):762-74.
4. Lagercrantz H. Connecting the brain of the child from synapses to screen-based activity. *Acta Paediatr* 2016;105(4):352-7.
5. Giuffrida F, Cruz-Hernandez C, Fluck B, Tavazzi I, et al. Quantification of phospholipids classes in human milk. *Lipids* 2013;48(10):1051-8.
6. Kamelska AM, Pietrzak-Fiecko R, Bryl K. Determination of cholesterol concentration in human milk samples using attenuated total reflectance Fourier transform infrared spectroscopy. *J Appl Spectrosc* 2013;80(1):148-52.
7. Delplanque B, Gibson R, Koletzko B, Lapillonne A, et al. Lipid quality in infant nutrition: current knowledge and future opportunities. J Pediatr Gastroenterol Nutr 2015;61(1):8-17.
8. Koletzko B, Agostoni C, Bergmann R, Ritzenthaler K, et al. Physiological aspects of human milk lipids and implications for infant feeding: a workshop report. *Acta Paediatr* 2011;100(11):1405-15.
9. Papathakis PC, Singh LN, Manary MJ. How maternal malnutrition affects linear growth and development in the offspring. *Mol Cell Endocrinol* 2016. Epub 2016 Jan 26.
10. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the essential composition of infant and follow-on formulae. *EFSA Journal* 2014;12(7):3760.
11. Birch EE, Castañeda YS, Wheaton DH, Birch DG, et al. Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. *Am J Clin Nutr* 2005;81(4):871-9.
12. Rodríguez-Cruz M, Tovar AR, Del Prado M, Torres N. Mecanismos moleculares de acción de los ácidos grasos poliinsaturados y sus beneficios en la salud. *Rev Invest Clin* 2005;57(3):457-72.
13. Fleith M, Clandinin MT. Dietary PUFA for preterm and term infants: review of clinical studies. *Crit Rev Food Sci Nutr* 2005;45(3):205-29.
14. Voet D, Voet JG. Bioquímica. 3.a ed. Buenos Aires: Panamericana; Metabolismo de los lípidos. 2006;Capítulo 25:945-1022.
15. Straarup EM, Lauritzen L, Faerk J, Hoy CE, et al. The stereospecific triacylglycerol structures and fatty acid profiles of human milk and infant formulas. *J Pediatr Gastroenterol Nutr* 2006;42(3):293-9.
16. Koo WW, Hockman EM, Dow M. Palm olein in the fat blend of infant formulas: effect on the intestinal absorption of calcium and fat, and bone mineralization. *J Am Coll Nutr* 2006;25(2):117-22.
17. González HF, Vicentin D, Giumelli O, Vazzano M, et al. Perfil de triacilgliceroles y porcentaje de ácido palmítico en la posición sn-2 en sustitutos de leche materna. *Arch Argent Pediatr* 2012;110(3):227-30.
18. Drisdel RC, Alexander JK, Sayeed A, Green WN. Assays of protein palmitoylation. *Methods* 2006;40(2):127-34.
19. El-Husseini Ael-D, Bredt DS. Protein palmitoylation: a regulator of neuronal development and function. *Nat Rev Neurosci* 2002;3(10):791-802.
20. Guirland C, Suzuki S, Kojima M, Lu B, et al. Lipid rafts mediate chemotropic guidance of nerve growth cones. *Neuron* 2004;42(1):51-62.
21. Koletzko B, Lien E, Agostoni C, Böhles H, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and

consensus recommendations. *J Perinat Med* 2008;36(1):5-14.
22. Auestad N, Scott DT, Janowsky JS, Jacobsen C, et al. Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. *Pediatrics* 2003;112(3 Pt 1):e177-83.
23. Hoffman DR, Birch EE, Birch DG, Uauy R, et al. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. *J Pediatr Gastroenterol Nutr* 2000;31(5):540-53.
24. Heird WC. The role of polyunsaturated fatty acids in term and preterm infants and breastfeeding mothers. *Pediatr Clin North Am* 2001;48(1):173-88.
25. Campoy C, Escolano-Margarit MV, Anjos T, Szajewska H, et al. Omega 3 fatty acids on child growth, visual acuity and neurodevelopment. *Br J Nutr* 2012;107(Suppl 2):S85-106.
26. Guesnet P, Alessandri JM. Docosahexaenoic acid (DHA) and the developing central nervous system (CNS) - Implications for dietary recommendations. *Biochimie* 2011;93(1):7-12.
27. McCann JC, Ames BN. Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *Am J Clin Nutr* 2005;82(2):281-95.
28. Carrié I, Clément M, de Javel D, Francès H, et al. Specific phospholipid fatty acid composition of brain regions in mice. Effects of n-3 polyunsaturated fatty acid deficiency and phospholipid supplementation. *J Lipid Res* 2000;41(3):465-72.
29. Farkas T, Kitajka K, Fodor E, Csengeri I, et al. Docosahexaenoic acid-containing phospholipid molecular species in brains of vertebrates. *Proc Natl Acad Sci USA* 2000;97(12):6362-6.
30. Sanhueza J, Nieto S, Valenzuela A. Ácido docosahexaenoico (DHA), desarrollo cerebral, memoria y aprendizaje: la importancia de la suplementación perinatal. *Rev Chil Nutr* 2004;31(2):84-92.
31. Birch EE, Carlson SE, Hoffman DR, Fitzgerald-Gustafson KM, et al. The DIAMOND (DHA Intake And Measurement Of Neural Development) Study: a double-masked, randomized controlled clinical trial of the maturation of infant visual acuity as a function of the dietary level of docosahexaenoic acid. *Am J Clin Nutr* 2010;91(4):848-59.
32. Hoffman DR, Theuer RC, Castañeda YS, Wheaton DH, et al. Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk. *J Nutr* 2004;134(9):2307-13.
33. Makrides M, Gibson RA, Udell T, Ried K. Supplementation of infant formula with long-chain polyunsaturated fatty acids does not influence the growth of term infants. *Am J Clin Nutr* 2005;81(5):1094-101.
34. Schulzke SM, Patole SK, Simmer K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev* 2011;(2):CD000375.
35. Jensen CL, Voigt RG, Llorente AM, Peters SU, et al. Effects of early maternal docosahexaenoic acid intake on neuropsychological status and visual acuity at five years of age of breast-fed term infants. *J Pediatr* 2010;157(6):900-5.
36. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. *Am J Clin Nutr* 2013;98(2):403-12.
37. Morse NL. Benefits of docosahexaenoic acid, folic acid, vitamin d and iodine on foetal and infant brain development and function following maternal supplementation during pregnancy and lactation. *Nutrients* 2012;4(7):799-840.
38. Gurnida DA, Rowan AM, Idjradinata P, Muchtadi D, et al. Association of complex lipids containing gangliosides with cognitive development of 6-month-old infants. *Early Hum Dev* 2012;88(8):595-601.
39. Timby N, Domellöf E, Hernell O, Lönnerdal B, et al. Neurodevelopment, nutrition, and growth until 12 months of age in infants fed a low-energy, low-protein formula supplemented with bovine milk fat globule membranes: a randomized controlled trial. *Am J Clin Nutr* 2014;99(4):860-8.