

Micronutrients and neurodevelopment: An update

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ABSTRACT

Micronutrients make up the central nervous system structure and play major functional roles: they stimulate nerve cell development, migration, and differentiation.

The goal of this study is to review the scientific literature regarding the role of micronutrients in infant brain structure and function. Thus, we aim at providing pediatricians with knowledge on the importance of introducing all nutrients into the diet based on breast milk composition. The following databases were reviewed: MEDLINE, through PubMed, TRIP Database, and LILACS.

An adequate nutrient supply, including calcium, copper, choline, iron, folic acid, iodine, and vitamins during pregnancy and lactation and in complementary feeding will have an effect on brain development and/or function.

Key words: *infant neurodevelopment, nutrition, breast milk, pregnancy, micronutrients.*

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INTRODUCTION

The development of the central nervous system (CNS) is a genetically determined, dynamic process which is modulated by a set of epigenetic factors.¹

An inadequate supply of some micronutrients may have a negative impact on brain structure or function.

In a previous review, we discussed the role of lipids on neurodevelopment.²

Knowing the composition of breast milk has made it possible to identify specific nutrients and their function. Specific deficiencies in some populations of malnourished children or experimental animal studies have guided knowledge on breast milk composition and its impact on CNS function and/or structure.^{3,4}

The goal of this study was to review the literature and update the knowledge on the potential benefits and mechanisms of action of micronutrients in relation to neurodevelopment. A bibliographic search was done using Medline,

through PubMed, TRIP Database, and LILACS for publications made between 2000 and 2016.

Choline

The proliferation, differentiation and migration of neural stem cells take place during embryonic development. Choline is involved in this whole process.⁵ It is a component of the phospholipid, phosphatidylcholine, and sphingomyelin membranes, and a precursor of the acetylcholine neurotransmitter.

It is the main source of methyl groups, necessary for deoxyribonucleic acid (DNA) and histone methylation. Choline metabolism is closely related to folate, vitamins B6 and B12, and methionine, and an alteration in any of these metabolic pathways is associated with changes in the others.⁶

Choline is involved in methionine synthesis from homocysteine. Choline deficiency during gestation determines the development of spina bifida, both in experimental animals and in humans. Choline supply to pregnant women has the following effects on their offspring: increases cell proliferation, reduces hippocampal apoptosis, increases neuron size, and improves learning and visual-spatial and auditory memory. The opposite occurs when there is choline deficiency.^{7,8}

Iron

Iron-deficiency anemia (IDA) is a public health problem that affects pregnant women and infants younger than 2 years old; in both populations, the CNS is highly-vulnerable.

It has been demonstrated that infants with IDA have worse results in mental and psychomotor developmental outcomes than children without iron deficiency. It

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has been shown that children with moderate IDA in the first months of life which is corrected after they turn 5 years old continue having a poor neurodevelopmental outcome.^{9,10}

The occurrence of IDA during brain development of experimental animals has resulted in a permanent reduction of iron content in the brain. Iron is essential for myelination, and it has been demonstrated that iron deficiency causes hypomyelination, permanent deficiency in the number of dopamine receptors, and neurotransmission worsening.^{9,10} A slower transmission has been observed in the brainstem auditory pathway of children with IDA, which is associated with hypomyelination.¹¹

Iron metabolism is closely related to docosahexaenoic acid (DHA) and has a major impact on neurodevelopment.¹²

Iron deficiency affects Δ -6-desaturase activity, i.e., the synthesis of essential fatty acids. Iron is a cofactor of stearoyl-CoA desaturase, which acts as a catalyst for the conversion of palmitic acid (16:0) into palmitoleic acid (16:1n-7), and of stearic acid (18:0) into oleic acid (18:1n-9), and acts in the initial and subsequent stages of essential fatty acid synthesis elongation, such as the synthesis of α -linolenic acid (18:3 n-3) into eicosapentaenoic acid (EPA) and DHA.¹³

Lactoferrin is a sialic acid-rich glycoprotein that carries human milk iron. It is associated with multiple benefits for health, including its ability to modulate immune function; but it is also very important because it facilitates milk iron absorption. Human milk contains significantly higher levels of lactoferrin than cow milk. According to a recent review of the role of lactoferrin, it seems to be an important nutrient for neurodevelopment, neuroprotection, and cognitive function during the rapid brain growth period. However, its mechanism of action has not been elucidated yet. There is also evidence of the specific benefits of lactoferrin, beyond the specific functions played by iron.¹⁴

Iodine

Iodine is an important micronutrient that is necessary for the production of thyroid hormone (TH). Severe iodine deficiency is one of the main preventable causes of mental retardation worldwide.¹⁵

The prevalence of severe iodine deficiency is very low thanks to iodized salt fortification. However, mild or moderate iodine deficiency is an alarming public health problem.^{16,17}

Pregnant women are susceptible to iodine deficiency because their iodine requirements double during pregnancy.¹⁸ Maternal free T4 provides T3 to the fetal brain and is necessary for the thyroid hormone-dependent neurodevelopment.¹⁸ Thyroid hormone nuclear receptors are present in the fetal brain as of 8 or 9 weeks of gestation and attain adult levels by week 18.¹⁹ After week 9, neural proliferation and migration towards the cerebral cortex, the hippocampus, and the medial ganglionic eminence start. At the beginning of the second trimester, fetal hormones develop but iodine reserves are very low, so maternal hormones supplement the necessary levels until birth. A low iodine maternal diet reduces the level of free T4, causes fetal hypothyroxinemia, and brain damage, which may later worsen due to fetal hypothyroidism. The most serious consequence is cretinism, which is characterized by a profound mental retardation.¹⁷ There is unequivocal evidence of the brain damage caused by severe iodine deficiency during pregnancy. However, there is no accurate knowledge on the damage caused by mild or moderate iodine deficiency or the effect of late supplementation during pregnancy. Some authors have demonstrated that iodine deficiency affects non-verbal intelligence quotient and reading skills.¹⁵ Breastfeeding women who use iodized salt may transfer adequate amounts of iodine to their infants through breast milk. Weaning is a period of risk for iodine deficiency because iodine requirements are high during childhood. Experts recommend against the use of salt (regular or iodized) and cow milk (a major source of iodine) during the first year of life. The prevalence of iron deficiency in this period is high and affects iodine metabolism.²⁰

Calcium

The most important pathway for the influx of Ca^{++} in excitable cells are voltage-dependent calcium channels (VDCC). VDCC open and allow the selective flow of Ca^{++} ions through the channels' pores; this results in a variety of intracellular processes, including neurotransmitter release, gene expression, modulation of membrane excitability, and neurite growth. Ca^{++} channels are the main bond between the electrical signals of membrane surface and intracellular biochemical responses.²¹

Ca^{++} is also involved, as a second messenger, in signal transduction, which controls neuron

and glial cell production. Neuroblasts derived from the neuroepithelium are the first precursors of glial and neuronal populations and, following neural induction, they have to grow and proliferate to produce a large number of cells and thus form the nervous system.²² Neuroblasts express cell-surface receptors; in turn, these become activated by their ligand, induce intracellular Ca⁺⁺ mobilization, and stimulate cell proliferation.²³ The inhibition of these receptors by their antagonists prevents Ca⁺⁺ mobilization and neuroblast proliferation.²⁴

Zinc

Zinc is a very important trace mineral for pre- and postnatal development.²⁵ Its functions are related to gene expression, cell development and replication, and ribonucleic acid (RNA) and DNA synthesis, which are critical for cell growth, differentiation and metabolism.²⁶ Zinc deficiency may affect cognitive development.^{27,28}

Zinc plays a structural and regulatory role in several enzymes, through signal transduction, pre-secretory polymers, and gene transcription systems, which are essential for metabolism, growth, and human reproduction. Zinc is involved in the main metabolic pathways of macronutrients, nucleic acids, heme synthesis, connective tissue replacement, gene expression, tissue synthesis, and embryogenesis. Some research studies observed a correlation between maternal levels of zinc and motor and cognitive neurodevelopment during early childhood; others found that zinc supplementation in pregnant women did not have any effect on subsequent neurodevelopment.⁸

COPPER

Copper is involved in hemoglobin formation and is essential for bone, tendon, connective tissue, vascular system, and myelin development and maintenance. Myelin is formed by phospholipids, whose synthesis depends on the cytochrome C oxidase, a copper-dependent enzyme. A lack of copper in the body manifests as moderate to severe anemia, edemas, bone demineralization, growth failure, anorexia, and vulnerability to infections. Copper is involved in ferroxidase activity, and may serve as the basis for an accurate control of iron flow to the different tissues.²⁹

Preterm infants and low birth weight infants are both populations vulnerable to copper deficiency. As is the case with iron and zinc, fetal hepatic copper accumulation occurs at the end of

gestation to supply copper for the first months of life, a period with minimum intake of this nutrient.³⁰

VITAMINS

Vitamin A

Retinoids are involved in the signaling pathway that regulates gene expression. They control neuron differentiation and the pattern of neural tube development. Retinoids are implied in synaptic plasticity, learning, memory, and sleep.³¹ These are essential molecules for sight, normal embryonic development, and control of cell growth, differentiation, and death.³²

Night blindness, anemia, and immunodeficiency are the main consequences of vitamin A deficiency. During pregnancy, it may cause teratogenic effects in body organs, such as the eyes, and the CNS. A manifestation of mild vitamin A deficiency is Bitot's spot. Severe vitamin A deficiency causes xerophthalmia, corneal ulcers, scarring and blindness.³³ Excessive exposure may also cause teratogenic effects and malformations, such as spina bifida, hydrocephalus, cleft palate, anophthalmia, and limb deformity.³⁴

Newborn infants' vitamin A deposits depend on breast milk to cover their needs and liver reserves. All mothers have reduced retinol levels in the first year postpartum, which progressively decreases vitamin A transfer from breast milk to the baby.³⁵ This reinforces the concept that it is necessary to provide vitamin A supplementation during lactation.³⁶

Vitamin B1

Thiamin (vitamin B1) is involved in carbohydrate synthesis and metabolism given that enzymes involved in this process require vitamin B to complete it. It also plays an important role in muscle contraction, nerve impulse conduction, and glucose absorption by the nervous system.³⁷

The brain stem, the cerebellum and the brain's limbic system are highly sensitive to vitamin B1 deficiency (pseudohypoxia), and its pathophysiology is similar to a continuous oxygen deprivation.³⁸

An incorrect vitamin B1 supplementation in soy-based formula showed that thiamin deficiency in infants causes encephalopathy, neuropathy, visual alterations, and death. Children who survive this type of deficiency have severe motor and cognitive sequelae and epilepsy.³⁹⁻⁴¹

Vitamin B6

Vitamin B6 must be obtained from the diet because humans cannot synthesize it. The main bioactive form of vitamin B6 is pyridoxal-5-phosphate. It is an essential cofactor for the functioning of more than 140 enzymes required for amino acid synthesis, breakdown and interconversion. It is a cofactor that limits dopamine, serotonin, gamma-aminobutyric acid (GABA), and noradrenaline synthesis. The synthesis of all these neurotransmitters is very sensitive to vitamin B6 levels. In addition, it has a direct effect on immune function, and gene transcription and expression, and plays a significant role in brain glucose regulation.⁴²⁻⁴⁴

Vitamin B9 (folic acid)

Vitamin B9 plays an important role in cell division, and amino and nucleic acid synthesis and is, therefore, essential for growth. It is necessary for the normal development of the fetal spine, brain and skull, especially during the first four weeks of gestation. It is critical for the synthesis of DNA, which transfers the genetic make-up, and RNA, which is necessary for protein and body tissue formation and other cell processes.⁴⁵

Folate coenzymes are necessary for the metabolism of important different amino acids, such as methionine synthesis from homocysteine. Folic acid deficiency is related to neural tube defects.^{46,47}

It is necessary for tetrahydrobiopterin synthesis and regeneration, an essential cofactor for the enzymes that turn amino acids into neurotransmitters (serotonin, melatonin, dopamine, noradrenaline, adrenaline), and nitric oxide.⁴⁸

Vitamin B12

Like the rest of the vitamins in the vitamin B complex, vitamin B12 is important for CNS metabolism and maintenance. Together with folate, it plays a significant role in homocysteine metabolism. It is essential for the preservation of the myelin sheath around neurons and neurotransmitter synthesis. Vitamin B12 deficiency causes damage in the myelin sheath covering cranial, spinal and peripheral nerves.⁴⁹ Vitamin B12 deficiency-related syndromes include myelopathy, neuropathy, neuropsychiatric disorders and, less frequently, optic nerve atrophy. Children with conditions related to hereditary cobalamin deficiency have

CNS damage characterized by a loss of white matter with delayed myelination.⁵⁰

Vitamin C

Vitamin C is an essential cofactor for numerous enzymatic reactions. Its functions include maintaining redox balance in the brain, modulating the cholinergic, catecholaminergic and glutaminergic systems, generally developing neurons through their maturation and differentiation, and forming myelin. In the developing brain, neuronal density and maturation are affected by vitamin C deficiency, which causes a reduced brain volume.⁵¹ Vitamin C deficiency also affects folic acid metabolism and iron absorption.⁵²

Vitamin D

1,25-dihydroxycholecalciferol induces the nerve growth factor (NGF), promotes neurite growth, and inhibits neuronal apoptosis in the hippocampus. Vitamin D deficiency during the prenatal period is associated with alterations in some CNS structures because it reduces the expression of certain genes involved in brain and cerebellar growth.

The vitamin D receptor is expressed in glial cells and neurons, induces the NGF, is a potent inhibitor of mitosis and a potent promoter of cell differentiation.⁵³

Vitamin D deficiency during neurodevelopment has been observed to cause behavioral, memory and learning disorders in adults.⁵⁴

Vitamin E

α -tocopherol is an antioxidant, maintains cell membrane integrity, and protects fat in low-density lipoproteins against oxidation. It is an essential compound for the adequate functioning and formation of the nervous system. It may cross membranes and enter into tissues, including the brain. Vitamin E deficiency is related to cerebellar ataxia, posterior cord medullary damage, and peripheral neuropathy. Ataxia due to isolated vitamin E deficiency is a familial, autosomal recessive disorder caused by a mutation in the gene that codes the α -tocopherol transfer protein.^{55,56}

FINAL COMMENT

An adequate diet in women of childbearing potential, and during pregnancy and lactation allows for an appropriate supply of the

micronutrients necessary for neurodevelopment. It is critical to get all nutrients. A single nutrient cannot be believed to provide a benefit without the balanced supply of all the others. Knowing these mechanisms strengthens recommendations.

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