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LITERATURE REVIEW

The role of prebiotics and nutrition in early stages for brain and socio-emotional development : A literature review

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Abstract

Introduction. The first 1000 days of life is the most crucial period for physical and neuro-emotional development. Since prenatal, the organ development had started and affected by many factors. Healthy neurodevelopment is dependent on socioeconomic, interpersonal and/or family, and nutritional factors. Macro- and micro-nutrients deficiencies may disrupt neurodevelopmental process. Iron, zinc, and iodium has been proven to affect brain development intrauterine and continues after birth. Prebiotics also play a role in neurodevelopmental through brain-gut-axis, but also beneficial on overall health.

Methods. Advanced search for relevant literatures in PubMed, Cochrane, and Willey was conducted. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Conclusions. Prebiotics supplementation is beneficial in promoting gut health, thus also play a role in immune pathway and influence brain function. Many studies also shown that prebiotics might be used as additional therapy in diseases that related to gut health i.e functional gastrointestinal disorders, obesity, and allergy.

Keywords early development, brain development, nutrition, prebiotics

Introduction

The cognitive, social and emotional parts of the brain continue to develop throughout the child's life. A large part of the ultimate structure and capacity of the brain is shaped early in life, before the age of 3 years, which known as the first 1000 days of life. The first 1000 days of life is undoubtedly the most important period that marked the beginning not only physical development but also socio-emotional development as well. Among the factors that influence early brain development is the provision of optimal nutrition. Nutrition is critical in supporting healthy brain development early in life, with long-lasting, and often, irreversible effects on an individual's cognitive development and life-long mental health Apart from macro-nutrients, micro-nutrients are also essential in brain development, which often overlooked in daily consumption. Prebiotics supplementation also plays an important role in which preclinical as well as clinical research has convincingly shown that early life nutrition can shape the gut microbiota and may affect brain development.

This review summarizes current knowledge on the brain and socio-emotional development in the early stages of life, and discussed the importance of prebiotics and nutrients in critical neuro-developmental windows.

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Methods

Advanced search for relevant literatures in PubMed, Cochrane Library, and Wiley Online Library was conducted on nutrition and prebiotic role in early brain development with time windows from 2000 to 2021. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Discussions

The first 1000 days of life development

The first 1000 days of human life started as early as in utero for approximately 270 days or 9 months and continues for another 730 days or until reaching two years of age.

Simultaneously with major body structures formation, such as spines, head, arms, and legs, human organs also began to develop since the very beginning. Digestive system, respiratory system, vascular system, urogenital system, and also nervous system begin to develop as early as the fetus reach 3 to 4 weeks old and the development continues during pregnancy, even after birth.

Brain development that occurs during the prenatal months is largely under genetic control, although clearly the environment can play a role; for example, it is well known that the lack of nutrition (e.g. folic acid) and the presence of toxins (e.g. alcohol) can both deleteriously influence the developing brain. In contrast, much of brain development that occurs postnatally is experience-dependent and defined by gene–environment interactions.[1,2]

The development of the different components of the nervous system intra-uterine can be categorized into distinct phases. These include the birth of neurons (neurogenesis), the migration of neurons to their correct location, the differentiation of neurons into different types and their subsequent maturation of connections, and the pruning back of connections and cells themselves. After birth, brain continue to grow and increase its mass during irregular periods commonly called growth spurts. This increase is most likely results from the growth of dendritic processes and myelination. Such an increase in cortical complexity would be expected to correlate with increased complexity in behavioral functions and also significant changes in cognitive development.[1,2]

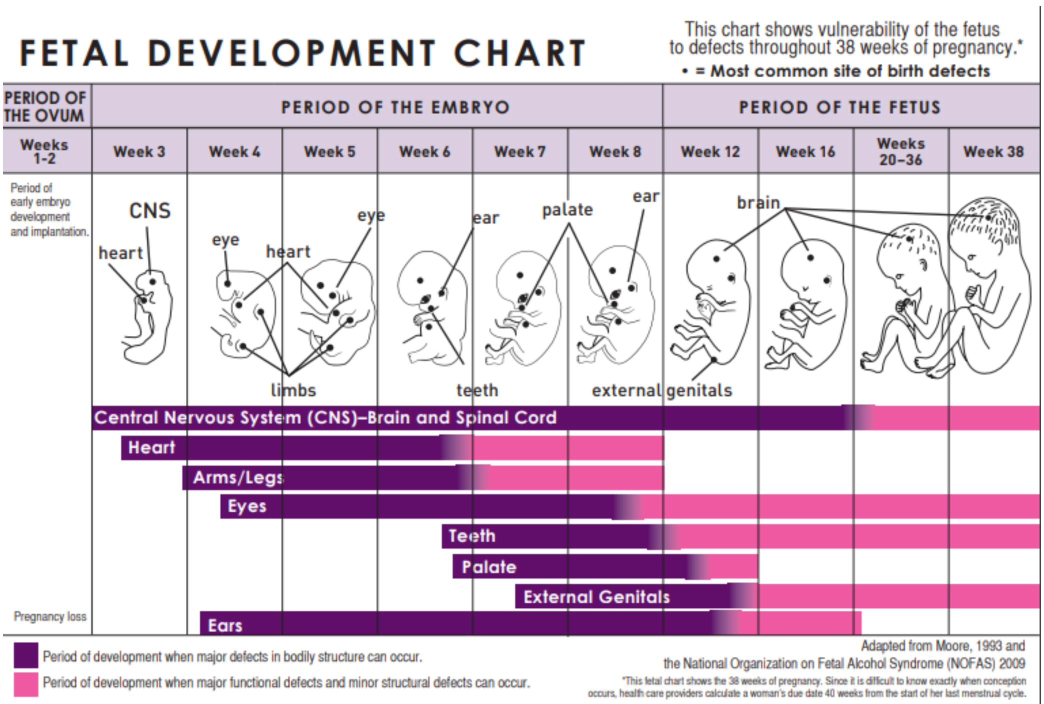


Figure 1. Fetal development chart

Brain development

The period of fetal life and the first 2 years postpartum may be seen as a time of tremendous opportunity for neurodevelopment and a time of great vulnerability. Healthy neurodevelopment is dependent on socioeconomic, interpersonal and/or family, and nutritional factors. The nutritional environment has an effect on whether brain growth and differentiation proceed normally or abnormally. Both adequate overall nutrition (ie, absence of malnutrition) and provision of adequate amounts of key macronutrients and micronutrients at critical periods in development are necessary for normal brain development. Importantly, the definition of malnutrition includes both undernutrition (provision of inadequate amounts of macro- and/or micronutrients) and also obesity (provision of excessive calories, often at the expense of other crucial nutrients). It is important to recognize that many nutrients exhibit a U-shaped risk curve, whereby inadequate or excessive amounts both place the individual at risk.[3]

Other factor that also play an important role in neurodevelopment is interaction between gut and brain, known as gut-brain axis. The brain-gut-microbiota axis is a complex interplay between the CNS, the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic arms of the autonomic nervous system, the enteric nervous system, and the microbiota. The communication throughout this axis is bidirectional, with brain signals affecting gastrointestinal tract motor, sensory and secretory functions, and simultaneous visceral signaling from the GI tract affecting brain function.[5]

Nutrition need in infants and children

A child's diet directly impacts on their growth and development, and later, also on their adult health. Achieving optimal intake will support optimal physical and socioemotional development, and prevent children from various diseases due to nutritional deficiencies. Many dietary recommendations available for children and most recommendation for those aged 2 years and older stress a diet that primarily relies on fruits and vegetables, whole grains, low-fat and nonfat dairy products, beans, fish, and lean meat. A varied and nutritious diet is recommended to assure optimal nutrition both macro and micro-nutrients.

According to Indonesian Recommended Dietary Allowance (RDA) based on age and gender, it is stated that calories needed are 550 kcal for 0–5 months of age, 800 kcal for 6-11 months of age, and 1350 kcal for age 2 to 3 years old per day. These calories estimation are based on a sedentary lifestyle thus increased physical activity will require additional calories from 10-14% per day. Indonesian RDA also continues to recommend diets low in saturated and trans fats. Daily intake should includes carbohydrate from grains, preferably whole grains; lean meat or legumes; vegetables; fruits; and dairy products or milk.

It was recommended that all infants should be breastfed exclusively for the first 6 months of life and continue until the age of 2 years. Breast milk not only meets the nutritional needs of young infants, but also confers other benefits. These include improved sensory and cognitive development, fewer infections, slower, healthier weight gain, improved maternal health, including a lower risk of breast cancer and endometriosis, greater postpartum weight loss and a lower maternal body mass index.[6,7,8]

Nutrition for brain development

All nutrients are important for brain growth and function, but certain ones have particularly significant effects during early development.

Macro-nutrients that affect early brain development are protein and long chain poly unsaturated fatty acids (LC-PUFA). Protein deficiencies manifested as growth failure, and in fetus known as intrauterine growth restriction. Preclinical models of early life malnutrition indicate that protein or protein–energy restriction results in smaller brains with reduced RNA and DNA contents, fewer neurons, simpler dendritic and synaptic head architecture, and reduced concentrations of neurotransmitters and growth factors. As for LC-PUFA, gestational and early postnatal LC-PUFA supplementation, particularly docosahexaenoic acid (DHA) and arachidonic acid, has been associated with improved cognition and attention in some studies. Preclinical models show that docosahexaenoic acid is important for neurogenesis and neuronal migration, membrane fatty acid composition and fluidity, and synaptogenesis. On animal models, LC-PUFAs showed a profound effect on visual system and areas of the prefrontal cortex that mediate attention, inhibition, and impulsivity. Willats 2018 and Oyen et al. 2018 prove that enrichment of diet with fatty acids has a positive impact on the child's learning skills, memory, language progress and cognitive competence in general. The insufficient intake of docosahexaenoic acid reduces DHA in the brain, leading to brain damage or abnormal brain disorder.[9,10,11,12]

Many micro-nutrients affect brain development such as zinc, iron, iodine, also vitamin B12, and vitamin D. Zinc is a vital nutrient for the brain, works as co-factor for more than 200 enzymes that regulate diverse metabolic activities in the body, including protein and DNA synthesis. It also plays a role in neurogenesis, maturation and migration of neurons as well as in synapse formation. Preclinical models indicate that zinc is necessary for normal neurogenesis and migration, myelination, synaptogenesis, regulation of neurotransmitter release in gammaaminobutyric acid-ergic neuron and ERK1/2 signaling, particularly in the fetal cortex, hippocampus, cerebellum, and autonomic nervous system. Behaviorally, early life zinc deficiency results in poorer learning, attention, memory, and mood.[9,10,13,14,15]

Iron is necessary for normal anatomic development of the fetal brain, myelination, and the development and function of the dopamine, serotonin, and norepinephrine systems. Iron also modifies the epigenetic landscape of the brain. Iron deficiency in early childhood is the most common micronutrient deficiency and can lead to irreversible damage to brain structure and cognitive function, regardless of therapies with iron supplements. Research has shown that iron deficiency can lead to delayed motor development, delayed cognitive processing, altered recognition, memory and executive functions and poorer emotional health later in the adult age. Positive impact of iron supplementation on cognitive function was observed in anemic primary school children.[15]

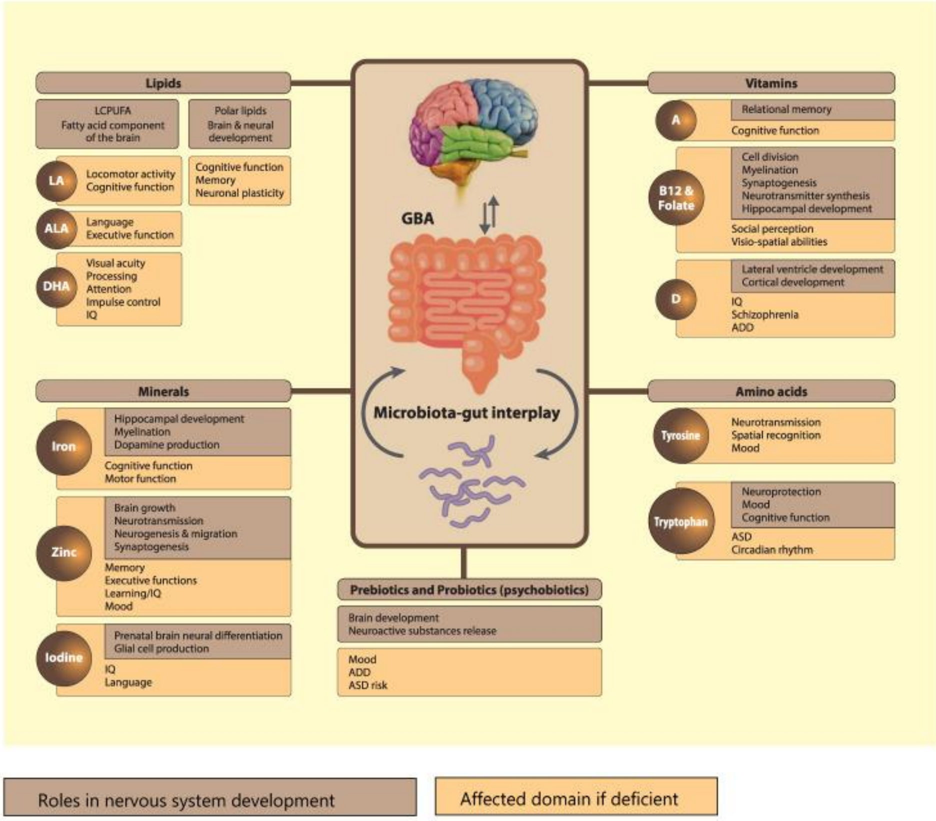
Iodine is an essential trace element for the biosynthesis of thyroid hormones. The developing fetal brain is most susceptible to iodine deficiency during the first trimester, when fetal triiodothyronine production depends entirely on supply of maternal thyroxine. Severe iodine deficiency during pregnancy is well-known to result in cretinism, marked by deficits in hearing, speech, and gait, and an IQ of approximately 30. Post-natally, iodine continues to play a role in neurocognitive development. The level of iodine in colostrum predicts the motor development capability of infants at 18 months.[15]

Vitamin B12 and vitamin D play a vital role in normal brain development and function.Vitamin B12 serves as a cofactor in numerous catalytic reactions in the human body, which are required for the neurotransmitter synthesis and functioning, and also essential in myelin production. Vitamin B12 and folate are required for cell division and generation of methionine, which is needed to produce neurotransmitters and myelin. Vitamin D deficiency in early pregnancy may correlate with delayed neurocognitive development, including language impairment, mental development and psychomotor development in early childhood. Interestingly, vitamin D also has been shown to be able to upregulate serotonin expression.[15]

Impact of prebiotic as nutrition intervention in children health

Another group of nutritional supplements that may be of interest as potential neuroprotective agents for preterm infants are prebiotics and probiotics. As the gut-brain axis concept becomes more familiar, more researches have been done and prebotics has been proven the benefit of maintaining gut health to better health and also beneficial for brain development.

The current definition of a prebiotic is the one proposed by the International Scientific Association for Probiotics and Prebiotics (ISAPP): a substrate that is selectively utilized by host micro-organisms and confers a health benefit. Prebiotics acting as a fuel source for selective fermentation by normal microorganisms in the gastrointestinal tract, which are required for protective effect against pathogens, or to improve intestinal barrier function, play a role



LCPUFA: long-chain polyunsaturated fatty acid; LA: linoleic acid; ALA: alpha-linolenic acid; DHA: docosahexanoic acid; IQ: intelligence quotient; ASD: autism spectrum disorder; ADD: attention deficit disorder; GBA: Gut-Brain Axis

Figure 2. Function of nutrients and prebiotics in brain development

in immune pathways and also influence brain function.[16,17]

These substance, which able to influence gastrointestinal health, comprise certain non-digestible oligosaccharides (NDOs), soluble fermentable fibres, and human milk oligosaccharides (HMOs). Human milk oligosaccharides are fraction of carbohydrate from human milk and they have been shown to selectively stimulate the growth of bifidobacteria and lactobacilli in the intestines. It is known that bovine milk is almost completely devoid of milk oligosaccharides, but recent biotechnical advances have made it possible to produce some synthetic milk oligosaccharides in large quantities. These advances enable supplementation of infant milk formula with the goal of promoting gut microbiota composition and function that is similar to that of a breast-fed infant. Preparations like galactooligosaccharides (GOS), fructooligosaccharides (FOS), 2'-fucosyllactose, lacto-N-neo-tetraose, inulin, oligofructose and galactofructose are examples of commonly used and studied products. These non-digestible oligosaccharides are widely used as additional supplementation because they provides the opportunity to improve the gut microbial ecosystem, including bacterial populations, biochemical profiles, and physiological effects. Prebiotic oligosaccharides have the potential to improve the infant's intestinal microbiota by promoting growth of Bifidobacteria, which may in turn reduce the burden of potentially pathogenic micro-organisms in the gut.[17,18]

Prebiotics also studied for their effect on neurodevelopmental. Gut microbiota affects the brain through three routes, including neural, endocrine, and immune pathways. The products of prebiotics fermentation can affect the brain by the vagus nerve. Some prebiotics, such as FOS and GOS, have regulatory effects on brain-derived neurotrophic factors, neurotransmitters (e.g., dserine), and synaptic proteins. Prebiotics also act as regulator for hormones such as corticosterone and adrenocorticotropic hormone, which in turn may affect mood and stress level. Schmidt et al. tested the intake of fructo-oligosaccharides (FOS) and Bimuno®-galactooligosaccharides (B-GOS), and reported that only B-GOS reduced the waking-cortisol response. Exaggerated waking cortisol is a biomarker of emotional disturbances, such as depression. Other studies on autisms shows that various prebiotics may have therapeutic effects on patients with autism by decreasing the population of Clostridium perfringens and increasing the rate of Bifidobacteria.[19,20,21]

An imbalance and/or reduced microbial diversity has been associated with a wide variety of functional gastrointestinal disease in children such as colic, irritable bowel syndrome (IBS), constipation and diarrhea, but also with other diseases such as allergy. In addition, many diseases later in life seem to be associated with the gut microbiota early in life, for example, inflammatory bowel disease, celiac disease, obesity, and allergic reactions. Prebiotics also shown to be beneficial as additional treatment in these diseases.[22]

Conclusion

Macro-nutrients such as protein and LC-PUFA and micro-nutrients supplementation such as iron, zinc, and iodium has been proven beneficial not only for health in general but for brain development as well. Prebiotics and probiotics supplementation also shown beneficial effect on health. Prebiotics safety profile and convinience in production and formulation process make it more favorable to be added in diets than probiotics. There are many studies on the positive effects of prebiotics on human health; however, accurately designed long-term clinical trials and genomics investigations are needed to confirm the health claims especially to determine whether prebiotics exert a beneficial effect on neurodevelopmental disorders in infants, and to understand the mechanism of action.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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