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Role of Nutrients in Cognitive Development of Children: A Review

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Abstract

Nutrients play an important role in the development of the brain and its cognitive domains. An insufficiency of nutrients in adults does not cause specific neurological damage, but among children, it may lead to problems associated with health, psychological behaviour and academic learning. In infants, deficiency of intake of certain nutrients such as iron, zinc and long-chain fatty acids has been associated with lower performance of cognitive tasks. This review highlights the role of various nutrients in the cognitive development of a child, as well as various measures to overcome nutrient deficiencies among children.

Keywords: Children, Cognition, Micronutrients, Nutrition

1. Introduction

A large body of research provides evidence that better-nourished children perform better in school[1]. Children require an adequate supply of nutrients for growth, energy and maintenance of body functions. The brain grows rapidly just before and for about 2 years after birth. So, the first two years of a child's life have been considered as very important[1,2]. A rapidly developing brain is more vulnerable to nutrient inadequacy and insufficiency. The brain has a limited capacity to store energy and therefore relies on energy and nutrients from the food we eat to help it develop and function. An adequate diet more specifically a diet including breakfast may improve brain function. Several micronutrients (vitamins and nutritionally essential minerals) have important biochemical roles in the brain and are needed for proper cognitive function. Cognition represents a complex set of higher mental functions sub-served by the brain and includes attention, memory, thinking, learning and perception[3]. Nutrients provide building blocks that play a critical role in cell proliferation, DNA synthesis, neurotransmitter and hormone metabolism and are important constituents of enzyme systems in the brain[3-7]. Brain development is faster in the early years of life compared to the rest of the body, which may make it more vulnerable to dietary deficiencies[8]. Cognitive development in preschoolers is predictive of school achievement in later years[9-11]. Deficiency of nutrients in children's diet affects not only the functioning of the brain but also cognitive development. This review highlights the role of various nutrients on brain functions and cognitive domains. Also, it suggests various methods for the prevention of nutritional deficiency and cognitive disorders.

2. Role of Key Macro and Micronutrients on Brain Function and its Cognitive Domains

Diet consists of two major food component groups: macro- and micronutrients which are classified according to their proportional amount in foods. Macronutrients are fat, proteins and carbohydrates whereas vitamins

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and minerals make up the class of micronutrients. Both groups of nutrients can affect brain and cognitive development which is reflected by outcomes such as mental performance, mood and behaviour as well as mental disorders[12,13]. Several studies show that diet plays an important role in the development and mental performance of a child[14-17]. As the brain develops and grows throughout childhood, one might expect greater demands on the provision of nutrition during periods of rapid growth which if deficient could impair brain structure development. This could have long-term consequences for mental functioning. For instance, brain development during childhood includes that of the frontal lobes - nutrition could affect frontal lobe development, influencing the higher cognitive functions they control (such as focusing attention and inhibiting irrelevant stimulation)[18]. On a more detailed level, certain nutrients can affect brain cell integrity and structures, signal transduction and neurotransmission as well as brain energy supply and metabolism[19]. Minerals mainly Iron, Iodine and Zinc are the major players (Table 1).

3. Macronutrients and their Role in Cognitive Development

3.1 Glucose

Glucose is the only metabolic fuel available to the brain. Glucose also enhances learning and memory in healthy-aged humans and enhances several other cognitive functions in subjects with severe cognitive pathologies including individuals with Alzheimer's syndrome and Down syndrome. It is required for the synthesis of neurotransmitters such as serotonin (5-hydroxytryptamine, 5-HT), noradrenaline (NA) and acetylcholine (ACH). The normal level of blood glucose is 4_ 5.5mmoll_1. This is controlled by a series of hormonal mechanisms. When it falls below 2.2mmol l, hypoglycaemia occurs. The decline in glucose, occurring in both mild and severe hypoglycaemia, impairs performance[20]. Subjective effects of neuroglycopenia (low blood glucose at the neuronal level) include negative mood (e.g. increased tension and anger) and attenuated arousal

Table 1. Summary of roles of key macro and micro nutrients in brain functions and its impact on cognitive domains

Nutrient	Role in Brain Function	Effect on Cognitive Domains
Glucose	Provides energy to the brain	depression effects overall mood state and psychological well being
Essential fatty acids n-3PUFA	it may influence neural functioning through its effects on proteins/ enzymes that play a role in brain membranes neuronal gene expression	delayed information processing
B vitamins	propagates nerve impulses	depression
Thiamin, folate and vitamin B-12	maintains the nerve's membrane potential helps in proper nerve conductance maintains integrity of the myelin sheath	episodic memory and language ability
Iron	proper development of oligodendrocytes (the brain cells that produce myelin) cofactor for several enzymes that synthesize Neurotransmitters	lack of memory and learning impairment lower cognitive scores, poorer motor development. altered social emotional development loss of brain iron compromises cognitive development.
Iodine	Neurocellular proliferation, synapse and dendritic formation.	lower IQ scores poor cognitive abilities – verbal knowledgenon-verbal and verbal abstract reasoning,visual spatial perception and executive functioning.
Zinc	essential to central nervous system and zinc containing neurons are concentrated in fore brain. zinc-dependent neurotransmitters in the mossy fibres system of the hippocampus are involved in memory.	deficits in attention learning ,memory and neuropsychological behavior.
Protein and Aminoacid like Tryptophan	precursor for the synthesis of neurotransmitter Serotonin.	affects mood and depression.

(e.g. drowsiness). Numerous reports suggest that memory is particularly affected by changes in glucose availability. Verbal memory and concept formation, in particular, are the most commonly affected cognitive functions in type II diabetes[20]. However, these functions are not impaired in experimentally induced hypoglycemia. A series of studies in elderly subjects showed that glucose enhanced (short-term) working memory[21].

3.2 Essential Fatty Acids

Due to its cellular composition, the brain contains a large amount (60%) of lipids[18]. Since the human body cannot efficiently synthesise Essential Fatty Acids (EFAs), they must be acquired from food. Consequently, the quantity and form of fats consumed may affect brain structure and functioning[12]. In recent years, there has been an increasing interest in the effect of EFAs, particularly Long-Chain Polyunsaturated Fatty Acids (LCPUFA), on cognitive development. Polyunsaturated Fatty Acids (PUFAs) omega-3 and omega-6, particularly Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA) are deemed to be of particular importance for brain development and function. For instance, a deficit in DHA can lead to a reduction of brain signalling by 90%[12]. The main mechanism behind the influences of omega-3-PUFAs on cognitive development and functioning seems to be through the maintenance of cell membrane integrity and cell compartment functioning in the Central Nervous System (CNS)[22]. During fetal development and the postnatal phase, a huge amount of PUFA and long-chain PUFA (LCPUFA) is deposited in the brain. Human breast milk contains n-3 and n-6 LCPUFA, and in addition, infant formulae have also been suggested[23]. While many clinical trials found an improvement of biochemical measures of LCPUFA status through supplementation[24], there is still no consensus about long-term neurological benefits from optimising the fatty acid status of infants during the pre-or postnatal phase[25]. However, at a later age, omega-3 provision has been associated with improvements in spelling, reading and learning in children with specific motor function impairments[26]. This is consistent with findings that show that brain areas responsible for this kind of higher-order cognitive function, such as the striatum and frontal cortex, are very rich in DHA[18]. Essential fatty acids play a central functional role in brain tissue. They are not only the basic components of neuronal membranes, but they modulate membrane fluidity and volume and thereby influence receptor and enzyme activities in addition to affecting ion channels. Essential fatty acids are also precursors for active mediators that play a key role in inflammation and immune reaction. They promote neuronal and dendritic spine growth and synaptic membrane synthesis, hence influencing signal processing and neural transmission[27]. In addition, they regulate gene expression in the brain[6]. The existing literature thus suggests that essential fatty acids are critical for brain development and cognitive function.

3.3 Proteins

Particularly during development, the brain needs a sufficient supply of amino acids for the synthesis of certain neurotransmitters (e.g. catecholamines, serotonin), The quality of dietary proteins influences the nature and the quantities of cerebral proteins and neurotransmitters and since the human body does not possess a reserve for proteins, essential amino acids have to be acquired from food every day[28]. One of those essential amino acids is tryptophan which is required as a precursor for the synthesis of the neurotransmitter serotonin. In addition to modulating appetite and satiety, serotonin also affects sleep and mood. Dietary tryptophan has been shown to affect mood and also on depression[28]. On a more general level, Protein-Energy-Malnutrition (PEM) has been identified as associated with stunting and impaired Intelligence Quotient (IQ) and school performance in children by cross-sectional studies[29]. Results show that PEM in early life has lasting effects up to 15 years of age on school performance and IQ scores which highlights the importance of adequate energy and protein supply in early life[18].

4. Micronutrients and their Role in Cognitive Development

4.1 Iron

Iron may play a critical role in cognitive development and later performance[30]. The brain tissue is rich in Iron. The most sensitive brain areas are the striatum, hippocampus and cortex. It is believed that iron is involved with different enzyme systems in the brain, including the cytochrome c oxidase enzyme system in energy production, tyrosine hydroxylase for dopamine receptor synthesis, delta-9-

desaturase for myelination and fatty acid synthesis, and ribonucleotide reductase for brain growth regulation[4,31-33]. In addition, iron appears to modify developmental processes in hippocampal neurons by altering dendritic growth[4,34]. An iron deficit can act globally on two different levels mainly a less efficient supply of oxygen to the brain and decreasing the activity of the enzyme cytochrome C oxidase in cerebral regions which leads to less energy production in the brain[4]. A decreased metabolic activity of brain cells is the consequence. Thus, all nervous cell types are affected and as a result, iron deficiency during early development perturbs cognitive functions in the long term[22]. Furthermore, if iron deficiency occurs very early in life, the damage may be irreversible, and it may not be possible to reverse this damage with iron treatment[35]. Other possible pathways could include functional changes of the brain, lags in the myelin formation or alterations in the dopamine system, particularly the dopamine receptors, or delay of the acquisition of motor skills due to constraints of oxygen supply in anaemic infants[18]. There is considerable evidence that iron deficiency or anaemia in children in developing countries is associated with impaired cognitive development[36].

4.2 Iodine

Iodine is required for the production of two thyroid hormones, triiodothyronine and thyroxine, both of which are essential for the development and growth of the brain[18]. A deficiency of either iodine or thyroid hormones (hypothyroidism) during critical periods of cerebral development induces not only a slowing of the metabolic activity of brain cells but also permanent alterations in the development of the brain. The most obvious sign of this impairment is irreversible mental retardation[22]. Iodine deficiency is considered the first cerebral disease in the world although being easy to prevent by iodine supplementation, especially during pregnancy when the brain development of the fetus is most rapid[22]. Iodine deficiency is anticipated to lower the IQ on average by 10 to 15 points at a general population level[37] with adverse implications for the socioeconomics of a community. The relationship between iodine and cognitive development is extensively researched. It is well known today that severe iodine deficiency during pregnancy may cause "cretinism" in children[38-40]. The clinical manifestation of cretinism depends on the severity of iodine deficiency. The features may include mental retardation, speech and hearing impairment, upper motor neuron and extrapyramidal lesions[37]. Iodine deficiency leads to hypothyroidism, leading to the underproduction of thyroid hormones which play an important role in neurodevelopment and various neurological processes including neuronal cell differentiation, maturation and migration, myelination, neurotransmission and synaptic plasticity[40].

4.3 Zinc

Zinc plays a role in a multitude of molecular and physiological mechanisms such as gene expression and protein synthesis. Even mild to moderate forms of zinc deficiency in children have been shown associated with reduced development and growth as well as impaired immune function[41,42]. An insufficient supply of zinc may affect cognitive development through alterations in activity, attention, motor development and neuropsychological behaviour. While the exact mechanisms are not identified yet, it is anticipated that zinc is vital for neurogenesis, neuromigration and synaptogenesis[18] which are all fundamental processes in brain function. In many parts of the world, zinc deficiency is likely to be a major public health problem[42].

4.4 Vitamin C (Ascorbic Acid)

This vitamin plays many roles. Ascorbic acid also has a subtle influence on the elaboration and functioning of nervous tissue, among others. Its presence is required for the transformation of dopamine into noradrenaline. Moreover, the biosynthesis of catecholamines occurs in tissues rich in ascorbic acid like the brain and the adrenal gland. At very high doses, as observed in rats, vitamin C even has an anti-stress effect. In the elderly, ingestion of vitamin C is associated with a lower incidence of major alterations in cognitive performance[43]. Others have reported a relationship between the serum level of vitamin C and IQ. This increases by four points when the plasma concentration of vitamin C increases by half. Some of the elements used in tests to determine IQ (non-verbal) are altered as a function of the serum concentration of vitamin C[44] and Vitamin C and its degenerative pathologies have been reviewed[45]. A regular intake of vitamin C reduces the risk of cataract[46]. The vitamin plays an important role in protection against different harmful oxidation reactions that involve molecular oxygen. Its properties as a reducing agent and its reaction with oxygen-derived free radicals seem to be its most important biological function.

4.5 Vitamin D

Vitamin D is currently under investigation in connection with the structure and function of the brain, since vitamin D or certain of its analogues are of interest in the prevention of various aspects of neurodegenerative or neuroimmune diseases[47]. Vitamin D protects the neurons of the hippocampus[48] and modulates the transport of glucose to the brain[49]. Its role in models of multiple sclerosis is under study as a result of recent positive findings, in particular concerning the duration and intensity of crises[39].

4.6 B-Vitamins

The B-vitamin group comprises vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3(niacin), vitamin B6 (pyridoxine), vitamin B9, which is known as folate or folic acid and vitamin B12 (cobalamin). While special emphasis is attributed to folate and its function in neural tube formation during embryogenesis, all B vitamins are essential for the normal functioning of the brain[22]. Vitamin B1 for instance facilitates the use of glucose, thus ensuring energy production in the brain. A deficiency of this vitamin results in severe diseases like beriberi with observed signs of lower intelligence and lassitude, which, however, are reversible[22]. The B vitamins folate, cobalamin and pyridoxine share a metabolic pathway that might have acute and long-term effects on the CNS[18]. It has been indicated that these vitamins influence cognitive performance through their role in methylation in the CNS which in turn affects the metabolism of neurotransmitters (e.g. dopamine, serotonin), all of which are crucial to psychological and neurological status[18]. Vitamin B12 has a role in axon myelination that is important for impulse conduction from cell to cell and it also protects neurons from degeneration. Vitamin B12 also alter the synthesis of different cytokines, growth factors and oxidative energy metabolites such as lactic acid[50].

4.7 Vitamin E (Tocopherol)

This vitamin particularly protects against ageing, especially in the brain, especially when combined with selenium. However, alpha-tocopherol also plays a role at the level of cognitive functions[51]. Vitamin E is, in reality, a mixture of numerous substances: tocotrienols and tocopherols (alpha, bêta, gamma, delta). Moreover, alpha-tocopherol has 3 asymmetric carbons and hence 3 different molecules. Each of these molecules is classically ascribed a coefficient of vitamin activity determined by various methods, either *in vivo* or *in vitro*. In terms of nutrition, only alpha-d-tocopherol and not gamma-tocopherol are bioavailable and integrated in biological membranes, including those in the brain[52]. The eventual specific roles of gamma-tocopherol are currently investigated. Nutritional Vitamin E deficiency alters brain fatty acid profile[53] (Clement 1993). Experimental Vitamin E deficiency induces retinal abnormalities[54]. In animals, early vitamin E supplementation in young but not aged mice reduces Abeta levels and amyloid deposition in a transgenic model of Alzheimer's disease[55]. High doses of vitamin E are proposed in the treatment of disorders of the CNS in the aged[56,57] and using antioxidant vitamin supplements (including vitamin E) reduces the risk of Alzheimer's disease[57]. The risk of dementia is significantly increased for the lowest vitamin E concentration compared to the highest (OR=2.54)[58]. Vitamin E may slow functional deterioration leading to nursing home placement[59]. At the molecular level, the tocopherols are extremely important. They have numerous roles, in particular, they neutralise the active and toxic forms of oxygen and scavenge free radicals. That is to say, they protect unsaturated fatty acids against peroxidation and thus contribute to maintaining the integrity and stability of cellular structures in the brain. They act in the lipid phase at a very low concentration (about one molecule per two thousand fatty acid molecules) and take part in a vast complex and interactive protective system, in cooperation with beta-carotene, vitamin A, vitamin C and various enzymes that function with selenium, copper, zinc and manganese. A distinct clinical syndrome (with paralysis) of combined vitamin E and vitamin C deficiency has been described in guinea pigs[60]. Interestingly, alternative nonantioxidant functions of vitamin E have been proposed, particularly as a "gene regulator"[61]. Tocopherols are found in substantial amounts in certain vegetable oils and eggs and small amounts in meat, tripes and cereal.

4.8 Copper

In brain ageing and neurodegenerative disorders, abnormal interactions of iron or copper with metal-binding proteins, such as neuromelanin or amyloid-beta peptide (Abeta), leading to oxidative stress, are important mechanisms. An unbalanced copper metabolism

homeostasis (due to dietary deficiency) could be linked to Alzheimer's disease[62].

4.9 Magnesium

Its deficiency is usually linked to spasmophilia, a state characterised by tetany without calcium being quantitatively low in the organism. The magnesium reserves (twenty-two grams in adults) are stored mainly in bone (more than half) and in skeletal muscle (one-quarter). The rest is distributed throughout the organism, especially in the nervous system. It has two roles, structural and metabolic. It is a stabiliser of the different compartments of the cell (organelles, such as the nucleus, or the mitochondria that produce energy, etc). Magnesium plays an important role in all the major metabolisms, oxidation-reduction, ionic regulation, etc. It activates about three hundred enzymes. In animals, the brain of magnesium-deficient rats is more susceptible to permanent focal ischemia[63]. Magnesium participates in the formation and use of chemical links rich in energy that are the basis of all biological activity in the cell. Magnesium is indispensable both for the synthesis and action of Adenosine Triphosphate (ATP) and most enzymatic reactions depending on ATP require magnesium, whether for carbohydrate, lipid, nuclear, or protein metabolism. Magnesium deficiency concerns up to one-fifth of the French population: 18% of men and 23% of women have intakes lower than 2/3 of the RDA and 77% of women and 72% of men have intakes lower than the RDA[64]. Magnesium intake is generally directly correlated with calorie intake. This is because most foods rich in magnesium also have high-calorie content, among the various possible sources, the magnesium in water and milk occupies a privileged position. It should be noted that milk is richer in magnesium than the high-magnesium mineral waters. Its bioavailability is also excellent. Other foods in order of decreasing magnesium content are whelks, winkles, snails (five times richer than oysters), haricot beans, walnuts, sorrel, lentils, mussels, spinach and beetroot[65].

4.10 Prevention of Nutritional Deficiencies

Since individuals consume combinations of foods which may contain other bioactive compounds that could act synergistically or antagonistically within or between food groups, it is important to investigate diet as a broadly encompassing variable in association with cognitive outcomes and research shows an association between diet and better health outcomes. It may be easier to implement changes in terms of dietary interventions[66].

In a further review by Whiteley *et al.*,[66] it was argued that several dietary interventions have been effective in attenuating the neurocognitive and other adverse psychological outcomes in developmental disorders. The authors focused specifically on an intervention involving the dietary elimination of gluten (the major protein in wheat, barley and rye) and casein (found in mammalian dairy products) and reported that this gluten and casein-free dietary intervention was effective in enhancing such functions as language, attention and motor control in individuals with autism spectrum disorders[66].

To prevent nutritional deficiencies the following three approaches are suggested:

4.10.1 Diversification

Increasing dietary diversity means increasing both the quantity and the range of micronutrient-rich foods consumed. Increasingdietary diversity not only improves nutrition but also improves the intake of many food constituents along with micronutrients. While adopting this process it should be ensured that dietary intakes of oils and fats are adequate to enhance the absorption of the limited supplies of micronutrients. The main limitation of dietary diversification is the need for behaviour change and education about how certain foods provide essential micronutrients and other nutritive substances. A lack of resources for producing and purchasing higher-quality foods can sometimes present a barrier to achieving greater dietary diversity, especially in the case of poorer populations.

4.10.2 Supplementation

Supplementation is the term used to describe the provision of relatively large doses of micronutrients, usually in the form of pills, capsules or syrups. It has the advantage of being capable of supplying an optimal amount of a specific nutrient or nutrients, in a highly absorbable form and is often the fastest way to control deficiency in individuals or population groups that have been identified as being deficient. In developing countries, supplementation programmes have been widely used to provide iron and folic acid to pregnant women and vitamin A to infants, children under 5 years of age and postpartum women. As a single high-dose vitamin A supplement improves

vitamin A stores for about 4–6 months, supplementation two or three times a year is usually adequate. However, in the case of more water-soluble vitamins and minerals, supplements need to be consumed more frequently.

5. Fortification

Food fortification refers to the addition of micronutrients to processed foods. Universal salt iodisation is an example of where this strategy has been used. Adding iodine to all salt has been a very successful way of preventing neurological complications caused by iodine deficiency. In societies with more resources and more centralised food distribution, fortification of flour with folate has been shown to decrease the occurrence of neural tube defects. In populations with restricted food choices, such as refugee populations in camps surviving on food rations, surveillance is needed to detect and correct vitamin deficiencies.

6. Necessary Measures for Preventing Cognitive Disorders

A large majority of malnutrition-related neurological disorders can be avoided by simple measures, such as the following recommended actions for policy-makers.

1. Support efforts towards universal salt iodisation.
2. Support vitamin A supplementation among children under five years of age, if necessary.
3. Consider strategies to decrease childhood malnutrition.
4. Consider folate fortification of flour, if affordable and possible.
5. Oversee the distribution of food rations to refugee populations, to detect and correct vitamin deficiencies.
6. Restrict alcohol consumption, especially during pregnancy.

A preventive approach should include adapted communication to change behaviour, strengthen capacities and reduce the incidence of some chronic diseases such as frequent neurological complications. Apart from this, education increases an individual's sense of personal control and self-esteem. These factors have also been shown to influence better health behavior[67,68]. The following activities are possible examples:

1. Specific nutritional programmes for children and pregnant and nursing women.
2. Rapid diagnosis of nutritional deficiencies in vitamins and minerals that could have a severe. impact on mother and child and alter their mental and physical status and development;
3. Nationwide measures such as those for the prevention of iodine deficiency and its consequences.
4. Awareness and education programmes for community members should be promoted.

7. Conclusion

Nutrients are critical for optimal brain development and function. Nutrition plays a crucial and complicated role in the development of the brain and cognitive function. Poor nutrition leads to the development of symptoms of neurological disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and dyslexia. Since nutrition is a modifiable factor, the optimal cognitive development and reduction of neurological disorders associated with nutrient deficiencies could be more easily regulated by adopting policy and programmes including food-based strategies such as dietary diversification and food fortification, as well as nutrition education, public health and food safety measures and finally supplementation.

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