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Perinatal and childhood nutrition and its impact
on cognitive function and adult diseases

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ABSTRACT: Maternal malnutrition, preterm birth, and childhood malnutrition may have an impact on physical growth and intellectual ability of affected children. Fetal and infant malnutrition can predispose to the development of type 2 diabetes mellitus, hypertension, insulin resistance, and cardiovascular diseases in adulthood. Maternal, infant, and childhood protein, folic acid, and vitamin B_{12} deficiency, and elevated homocysteine levels could impair metabolism of essential fatty acids and cause decrease in the concentrations of their long-chain metabolites: arachidonic, eicosapentaenoic, and docosahexaenoic acids and their metabolites. These metabolic derangements may cause cognitive impairment, endothelial dysfunction, susceptibility to various infections, and low-grade systemic inflammation that predisposes to the development of insulin resistance, type 2 diabetes, hypertension, and cardiovascular diseases. Since these nutrient deficiencies are more common in low to middle income families of developing countries, it is essential that effective measures are implemented to prevent impaired physical growth, cognitive function and adult diseases. Even in the developed countries malnutrition in the form of overnutrition may have similar consequences. Hence ensuring optimal nutrition during pregnancy, lactation, infancy, childhood, and adolescence is essential to ensure physical, mental, and psychological wellbeing of the growing children so that the development of adult diseases are prevented or postponed and this, in turn, reduces the burden of diseases on the health care system of the nation.

INTRODUCTION

Malnutrition can be both undernutrition and overnutrition. Undernutrition is a deficiency of calories or of one or more essential nutrients. Undernutrition is due to deficiency primarily of calories (that is, overall food consumption) or of protein. Deficiencies of vitamins and minerals though usually considered separate disorders, in majority of the instances, when calories are deficient, vitamins and minerals are likely to be also. Undernutrition, which is often used interchangeably with malnutrition, is actually a type of malnutrition. Malnutrition is an imbalance between the nutrients the body needs and the nutrients it gets. Thus, malnutrition includes overnutrition i.e. consumption of too many calories or too much of any specific nutrient-protein, fat, vitamin, mineral, or other dietary supplement, and this is common in the developed world especially excess consumption of calories from fat. In developing countries, protein-energy undernutrition is common especially in children. Marasmus is a severe deficiency of calories and protein and tends to occur in infants and very young children, and it typically results in weight loss and dehydration, whereas Kwashiorkor is a severe deficiency more of protein than of calories. Breastfeeding usually protects against marasmus. In recent years, marasmus and kwashiorkor are less common whereas suboptimal nutrition due to inadequate nutrient intake, excessive nutrient losses or increased metabolic requirements is more common. In the present discussion, the terms malnutrition and undernutrition are used interchangeably for the sake of convenience. Since severe malnutrition is uncommon in the developed and developing countries except in some countries of Africa, the term malnutrition used here refers to mild to moderate undernutrition. It is known that malnutrition causes stunted growth, decreased muscle mass and strength, and smaller internal organs (such as kidneys with decreased number of glomeruli, relatively less number of pancreatic β cells, etc.), which are well known. In the present discussion, emphasis is on the less well recognized consequences of undernutrition such as its impact on cognitive function and risk of development of adult diseases.

ANATOMICAL CHANGES IN THE BRAIN DUE TO UNDERNUTRITION/MALNUTRITION

Protein energy malnutrition stunts brain growth and thereby has a direct, independent effect on brain function. Since protein energy malnutrition coexists with other nutritional deficiencies and imbalances that not only divert development from a normal trajectory but also affect central nervous system (CNS) function. Furthermore, brain development could be affected by nutrient interactions and other health status variables. Recent evidences suggest that even the most prevalent levels of general undernutrition represent a risk factor that increases the probability of deviating human development from its normal trajectory and thus, could influence not only cognitive function but also development of adult diseases. Malnutrition endured during certain sensitive periods in early development could produce irreversible brain damage possibly resulting in mental retardation and impairment in brain function. Most of the alterations in the growth of various brain structures eventually recover, although permanent alterations in the hippocampus and cerebellum remain.

Neuropharmacological studies revealed that long-lasting changes in brain neural receptor function could occur due to early episode(s) of malnutrition. The fact that marginal undernutrition affects almost half the world's children that might permanently limit their intellectual capacity to function in a technologically advancing world are clearly frightening (1). It is known since early 1960's that malnutrition during early life reduces the growth of the brain and impairs its functional capacity (2-5).

Malnutrition in early life produced a reduction in the volume of the cerebral cortex, the brain region most closely linked to cognitive and intellectual function. Although, the number of cortical neurons is not affected suggesting the remarkable capacity of neural plasticity it can be described in pathologic terms as cell packing (6-11). Malnutrition causes a significant disruption in pyramidal cells of the cerebral cortex (12), reduction in the density of cortical dendritic spines (13), a decrease in the width of cortical cells (14) and the complexity of the dendritic branching of the cortex (15, 16). In addition, the total number of cortical glial cells, the total number of synapses in visual cortex, the length and the width of synaptic reactive zones, and the number of cisterns embedded within the spinous apparatus are reduced by malnutrition (17-19). Most of these abnormalities revert to normal following adequate nutrition subsequently, except that the reduced ratio of granule: Purkinje cells remains abnormal.

FUNCTIONAL CHANGES IN THE BRAIN DUE TO UNDERNUTRITION

The structural changes seen in the brain due to undernutrition predicts that children will be intellectually damaged as a result of anatomical perturbations. For instance, electrophysiological studies revealed that experimental animals have a decrease in excitability and diminished ability of parietal and prefrontal cortical neurons to repetitive pulses (20, 21). This diminished cortical response persists despite nutritional recovery. This diminished sensitivity of cortical structures to basal stimulation is abolished by the administration of propranolol, a β blocker (22) suggesting that undernutrition produces long-term alterations in neurotransmitter metabolism at the receptor level.

CHANGES IN THE NEUROTRANSMITTERS

Pre- or postnatal malnutrition causes an increase in brain concentration of the monoamines, serotonin and norepinephrine (23, 24), though others have found a decrease in monoamines. In most cases, however, brain levels of these amines revert to normal after nutritional rehabilitation, though this has been disputed. For instance, a reduction in the number of norepinephrine receptors was noted that explains the decreased activation seen after administration of adrenergic drugs (25-27).

A lack of responsiveness to psychopharmacological challenges is one of the hallmarks of early malnutrition such as lack of an amnesic effect after β-endorphin administration and milder withdrawal syndrome in response to naloxone administration in opiate treated rats. Similarly, behavioral response to anxiolytic drugs is also blunted in previously malnourished but nutritionally rehabilitated animals. Thus, there is a depressed reaction to noradrenergic, serotonergic and GABA-ergic drugs, though no change in their behavioral response to caffeine or to amphetamine was noted (28-30).

Hippocampus is adversely affected by early malnutrition. Some of the observed effects include: (i) a significant reduction in the size of cells of the dentate gyrus, (ii) a reduction in the degree of dendritic branching, and (iii) a decrease in the number of granule cells. A functional measure of the hippocampus revealed that though the number of synapses per neuron is not affected by early postnatal malnutrition, there are significantly fewer synapses per neuron after nutritional rehabilitation at the end of 75 days of rehabilitation; whereas after ~ 130 days and 250 days of rehabilitation the number of neurons per synapse decreased in the controls and continued to increase in the previously malnourished rats. The fact that the malnourished animals accumulated ~ one-third more synapses per neuron than the well-fed controls could explain the functional abnormalities seen in malnourished animals and humans. It is possible that the abnormal number of synapses per neuron observed could lead to dysregulation in neurotransmission and consequent functional abnormality. This is supported by the observation that the firing pattern of hippocampal neurons is altered by early malnutrition. Furthermore, malnourished animals fail to show long-term adaptation and exhibited significantly diminished long-term potentiation (LTP), a marker of cognitive function and memory formation (31-33).

These studies suggest that malnutrition endured during certain sensitive periods in early life affects brain development that could produce irreversible brain damage, possibly resulting in mental retardation and impairment in brain function. Although, much of the alterations in the growth of various brain structures caused by malnutrition eventually recover permanent alterations in the hippocampus and cerebellum remain, long-lasting alterations in brain neural receptor function may occur, and these alteration may lead to behavioral abnormalities and cognitive function impairment including emotional response to stressful events. Evidence suggests that there could be subtle deficits in long term memory function. Small deficits in IQ have consistently been found in previously malnourished humans, and that they may have attentional dysfunction and impulsivity, a behavioral pattern indicative of deficits in executive functioning (34).

In this context, it is interesting to note that at present more children are encountering marginal to moderate undernutrition especially for zinc, folic acid, vitamin B_{12}, and polyunsaturated fatty acids (PUFAs) that are essential for brain development and growth. Furthermore, marginal to moderate undernutrition is not uncommon in the elderly population.

POLYUNSATURATED FATTY ACIDS, FOLIC ACID, VITAMIN B_{12} AND THEIR ROLE IN COGNITIVE FUNCTION

Recently ω-3 fatty acids, especially docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and ω-6 arachidonic acid, present in human milk, were shown to be necessary for retinal and brain development in primates and humans. Rod photoreceptor function and the maturation of visual acuity of human low birth weight (LBW)

infants are dependent on the supply of these essential nutrients. Visual function of full-term infants fed human milk is enhanced for up to 3 years, supporting the concept of long-term benefits of human milk feeding on mental development. The LBW infants who received human milk showed higher IQ at age 8 years. Since human breast milk is a rich source of AA, EPA, and DHA, these beneficial effects have been attributed to these fatty acids (reviewed in 35-38).

Risk of dementia or cognitive impairment is high in the elderly who have elevated homocysteine levels (39). Daily supplementation of 800 μg of oral folic acid for 3 years increased serum folate concentrations, reduced plasma total homocysteine levels, and improved cognitive function (40), suggesting that a close association exists between folic acid, homocysteine and cognitive function. Oral folic acid supplementation to healthy human volunteers not only restored endothelial nitric oxide (eNO) synthesis but also prevented nitrate tolerance to continuous treatment with nitroglycerine by restoring and/or stimulating endogenous generation of tetrahydrobiopterin (H_4B), an essential co-factor for NO synthesis (reviewed in 41, 42). Furthermore, folic acid increases concentrations of ω-3 PUFAs (polyunsaturated fatty acids) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (41, 42) that are known to be useful in the prevention/treatment of dementia and Alzheimer's disease (54, 55). Both EPA and DHA enhance NO generation, suppress production of pro-inflammatory cytokines, and enhance brain acetylcholine levels, a neurotransmitter whose levels are decreased in Alzheimer's disease (reviewed in 41, 42). In addition, folic acid could enhance the formation of neuroprotectin D1, an anti-inflammatory and cytoprotective molecule from DHA and lipoxins and resolvins from EPA, DHA, and arachidonic acid (AA) by virtue of its ability to enhance plasma levels of these PUFAs. In a population-based survey of New Zealanders, a strong and consistent association between EPA in serum phospholipids and self-reported physical well-being was noted (43). In the elderly, a diet high in fish and fish products is associated with better cognitive performance in a dose-dependent manner (44); and higher plasma n-3 PUFA proportions were associated with less decline in the speed-related cognitive domains over 3 years (45). These results coupled with the observation that low serum vitamin B_{12} status but not folate predicted more rapid cognitive decline (46) suggests that marginal deficiencies of these nutrients enhance the risk of dementia and Alzheimer's disease.

It was reported that north Indian preschool children have low plasma cobalamin and folate concentrations and elevated total homocysteine and methylmalonic acid concentrations (47). The report from India is particularly disturbing since it is known that low serum folic acid and vitamin B_{12} concentrations may lead to rapid decline in cognitive function, are associated with elevated plasma homocysteine concentration that can cause endothelial dysfunction, a precursor of enhanced cardiovascular risk; and these nutrient deficiencies may be associated with low plasma and tissue AA, EPA, and DHA concentrations. The incidence of preterm birth is high in developing countries and so it is expected that these infants have low plasma concentrations of AA, EPA, and DHA since preterm infants have limited ability to form AA, EPA, and DHA from dietary precursors due to decreased activities of enzymes Δ^6 and Δ^5 desaturases (48-50).

This implies that preschool children of low to middle income families may have low cognitive function due to decreased plasma folic acid, vitamin B_{12}, and AA, EPA, and DHA concentrations that may also explain the emerging epidemic of cardiovascular diseases in the developing world especially India and China since these fatty acids prevent coronary heart disease. Furthermore, in the developed world Alzheimer's disease is assuming epidemic proportions due to ageing of the population, and so it is important that more studies are needed wherein in plasma folic acid, vitamin B_{12}, and AA, EPA, and DHA concentrations are measured simultaneously in the study population to define their role more precisely in cognitive function. Since in developing countries almost half the population belongs to low to middle income group, it is likely that as the population ages the incidence of Alzheimer's and cardiovascular diseases may become more common that could have enormous socio-economic implications. In view of the role of folic acid, vitamin B_{12}, and AA, EPA, and DHA both in Alzheimer's disease, and cardiovascular diseases (41, 51, 52) it remains to be seen whether their prophylactic administration might prevent these diseases.

INFANT AND CHILDHOOD NUTRITION AND ADULT DISEASES

Stimuli or insults during the perinatal period can have lifetime consequences and is called as "programming". Programming stimuli may be generated endogenously or environmental.

Early nutrition is one important environmental signal that can induce lifetime effects on metabolism, growth, and neurodevelopment and on major disease processes such as hypertension, diabetes, and obesity (reviewed in 53). This is supported by the observation that exclusive breast-feeding, an early environmental stimulus, protects against the development of adult diseases: insulin resistance, obesity, hypertension and type 2 diabetes mellitus, and decreases the risk of coronary heart disease (CHD) in later life (53). A high prevalence of obesity was reported in those who were of either low or higher birth weight, which depends on the maternal diet. Heavier mothers had heavier babies and these babies went to have a high BMI (body mass index) in adult life. People who were small babies tend to have a more abdominal distribution of adipose tissue, a significantly reduced muscle mass, and a high overall body fat content in adult life, suggesting that nutrient supply in early pregnancy is a significant factor influencing the development of obesity in adult life. It has been suggested that early nutrition programmes the appetite regulating centers. Hypothalamic appetite regulatory centers develop predominantly after birth (though they can also be expressed before birth (14)), suggesting that

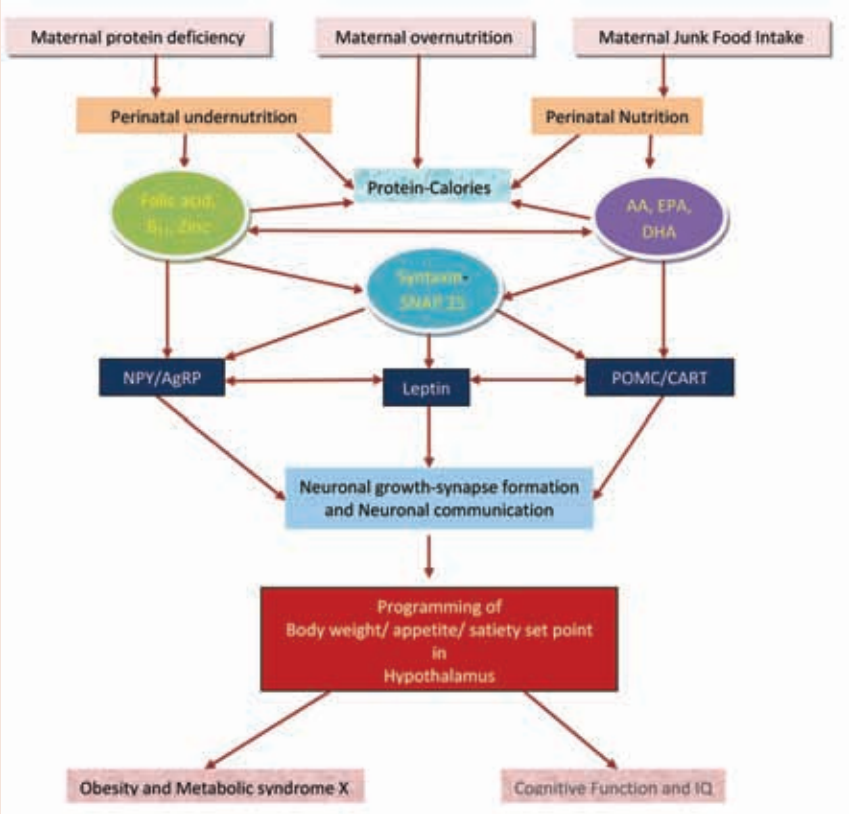

Figure 1. Scheme showing the relationship between perinatal and childhood nutrition and cognitive function and IQ and metabolic syndrome X in adult life. For further details see text

factors that influence brain growth and development will have substantial impact on the development of appetite regulatory centers that, in turn, determine subsequent food intake in later life. For instance, postnatal over nutrition in rats led to an increased early weight gain and fat deposition, hyperphagia, obesity, hyperleptinemia, hyperglycemia, hyperinsulinemia and insulin resistance and these over fed rats showed decreased mean areas of neuronal nuclei and cytoplasm within the paraventricular (PVN), ventromedial (VMN), and arcuate (ARC) nuclei of hypothalamus and a significant increase in the number of NPY containing neurons within the ARC and decreased immunostaining for both POMC and α-MSH (65). These results indicate that neuropeptides that regulate appetite centers and their responses to stimuli such as glucose, insulin and other stimuli is "programmed" in the fetal and perinatal stages of development. This implies that factors that govern the growth and development of brain and biochemical stimuli such as glucose, insulin and fatty acids (both saturated and unsaturated fatty acids that may include both short chain and long chain fats) that influence the development of various hypothalamic neurons may have long-lasting impression or programming affects on the appetite regulating centers. This ultimately could influence the dietary preferences and the development of obesity in later life.

POLYUNSATURATED FATTY ACIDS AND NEURITE OUTGROWTH

Brain is rich in polyunsaturated fatty acids (PUFAs): arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which constitutes as much as 30 to 50 percent of the total fatty acids in the brain, where they are predominantly associated with membrane phospholipids. For proper neuronal development and increase in cell membrane surface area, growth of neurite processes from the cell body is critical. Nerve growth cones are highly enriched with AA-releasing phospholipases, which have been implicated in neurite outgrowth. Syntaxin 3, a plasma membrane protein that has an important role in the growth of neurites, is activated by AA, DHA and other PUFAs. Furthermore, AA stimulated syntaxin 3 to form the ternary SNARE complex (soluble N-ethylmaleimide-sensitive factor attachment protein receptor), which is needed for the fusion of plasmalemmal precursor vesicles into the cell surface membrane that leads to membrane fusion. These results imply that when the concentrations of PUFAs are inadequate, during the critical period of brain growth development and maturation, it could lead to inappropriate synaptic connections of hypothalamic neurons. Hence, undernutrition and deficiency of PUFAs and folic acid and vitamin B_{12}, and zinc during infancy and childhood could lead to hypothalamic dysfunction and predispose them to develop metabolic syndrome X during adult hood. Furthermore, AA and EPA/DHA feeding enhanced the expression of POMC in hippocampus suggesting that PUFAs influence appetite and satiety and thus, control energy metabolism. AA and DHA influence the expression of dopamine receptor genes and their products, modify monoaminergic neurotransmitters in frontal cortex and hippocampus, and facilitate release and actions of GABA and acetylcholine lending support to the concept that PUFAs have a modulatory influence on the release, action and properties of various neurotransmitters in the brain (53). Both protein deficiency and high-energy diet decreases the formation of EPA, DHA and AA. Thus, maternal malnutrition and low perinatal PUFAs could lead to the development of obesity and metabolic syndrome X in adulthood (Figure 1). Junk food is known to be energy dense and rich in saturated and trans-fatty acids that leads to PUFA deficiency in the mother and offspring. Thus, perinatal deficiency of PUFAs could lead to the development of obesity and metabolic syndrome X due to programming of the "body weight/ appetite/ satiety set point" set at a higher level. This is supported by the observation that development of obesity occurs in the offspring due to maternal junk food intake during pregnancy and lactation. This implies that supplementation of PUFAs during this critical period of growth could prevent the development of obesity and metabolic syndrome X in childhood and adult life (53).

CONCLUSIONS

Nutritional factors such as AA, EPA, and DHA, folic acid, vitamin B_{12}, and zinc are essential for brain growth and development, formation of appropriate synaptic connections, and normal cognitive function. These nutritional factors coupled with adequate provision of protein, carbohydrate and fat in the diet would ensure normal structure and function of the brain. Inadequacy of any one of these factors is expected to result in subnormal or abnormal brain growth and function. In the developed countries such as USA and Europe though undernutrition is uncommon, surprisingly inadequacy of folic acid, vitamin B_{12} and EPA and DHA has been documented, especially in the elderly and obese children. The inadequacy of EPA and DHA is, in part, due to the consumption of excess of saturated fat, trans-fats and ω-6 fats. On the other hand, in the developing world, frank deficiency of folic acid, vitamin B_{12}, and AA, EPA, and DHA is common. Thus, in both the developed and developing countries inadequacy of dietary essential nutrients for proper growth and development of the brain and its function seem to be not uncommon. But the inadequacy of these essential nutrients is more acute in the developing world since children in these countries also have protein-calorie malnutrition. Almost half of the children in the world are at risk of mild to moderate undernutrition and hence, are specifically vulnerable to brain dysfunction and could have mild to moderate degree of cognitive

impairment and emotional and behavioral changes (see Figure 2). In the present world of ever changing technology and fast pacing knowledge, if half of the children in the world were to have even mild cognitive impairment, and behavioral and emotional disturbances, it will have a great impact on the development of the countries involved since these children as adults will not be able to contribute adequately to the economy and development of the country in which they live. This is likely to have a major impact on the economic prosperity of the country (ies) and the world in general.

This impact is most on developing countries in which nutritional inadequacies are common. Hence, provision of adequate amounts of the nutritional factors such as PUFAs, folic acid, vitamin B_{12}, and zinc in addition to appropriate amounts of proteins and calories to the growing children is a must and should receive immediate priority not only to reduce impairment of cognitive function but also of the future development of various adult diseases.

Figure 2. Summary of the effects of perinatal malnutrition on children

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