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Asindi AA

Nutritional iron and childhood intellect

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Asindi AA (✉)
Department of Paediatrics,
University of Calabar, Nigeria
Email: asindi.asindi@yahoo.com

Abstract*:* Iron deficiency is the most prevalent micronutrient malnutrition globally. It is known to affect both children and adults especially pregnant women largely in the developing countries. Iron is not only important for haemoglobin synthesis but also for normal brain development. In the body, the ferrous formis converted into ferritin which is the active molecule. The brain is especially sensitive to variation in iron availability, in part due to the high metabolic demands of the brain that are supported by iron. Iron is necessary for basic neuronal processes such as myelination, neurotransmitter production, and energy metabolism. With neuroimaging support, Globus pallidus, caudate nucleus, putamen, substantia nigra and the hippocampus have been of primary interest in studies of iron because they show robust and quantifiable levels of iron content. Furthermore, these regions are central to cognitive abilities that develop across childhood and adolescence, such as processing speed, cognitive-motor control, reward-processing, and working memory function. The hippocampus per se plays important roles in the consolidation of information from short-term memory to long-term memory, and in spatial memory that enables navigation.
Low iron levels in pregnant women correlates with low ferritin levels in their foetus and newborns whereby several studies have clearly demonstrated the effect of iron on developmental milestone regarding cognition and behaviour. Iron deficiency early in life, therefore, confers irreversible brain dysfunction even after complete brain iron repletion. Iron therapy and replenishment of brain ferritin may revert to normal cognitive functions in adults and adolescents but not in children. Rich sources of iron are meat, liver, dark leafy green vegetables, fish, poultry, peas and beans. Pregnant women require routine daily iron supplement; lactating woman and all children should be fed balanced diet. Special iron supplement should be provided for preterm and small-for-gestational-age infants from the age of two months.

Keywords: Iron deficiency, childhood, Intellectual impairment.

Introduction

Iron deficiency (sideropenia) is the most prevalent nutrient deficiency in the world afflicting an estimated 2.5–5 billion people.[1,2] It is more common in developing countries where 46–66 per cent of all children under 4 years of age are anaemic.[3-5] More than 50 per cent of paediatric anaemia in the developing countries can be attributed to iron-deficiency with a peak prevalence among those in the 6-24 months age bracket.[9] Maternal sideropenic anaemia complicates 30–50 per cent of pregnancies in developing countries; in contrast, in developed countries where iron supplements are routinely administered, this figure is less than one percent.[5] The most common cause of foetal/neonatal iron sideropenia is maternal iron deficiency. Infants born to mothers suffering from iron-deficiency anaemia have lower iron levels and are more prone to anaemia.[5]

Dietary iron is converted to ferritin which is the active form of iron in the body. Apart from haemoglobin synthesis, ferritin is a necessary element in the development and functioning of the nervous system. Infants and children with low ferritin levels are at riskof impairment of brain development and function.[3, 6-8]

Because iron is involved in the function of various enzymes and neurotransmitters in the central nervous system hence low serum levels of ferritin is postulated to lower seizure threshold, including febrile convulsions.[9] Restless Legs Syndrome appears to be related to deficits in brain iron content and metabolism.[10] Other conditions associated with deficeit in brain iron contents and metabolism in children and adolescents include syncope,[11]stroke,[12] affective respiratory crises,[13,14] and schizophrenia.[15]
This review focuses on what impact iron deficiency

hason the intelligence of children.

Neurobiology and neurophysiology of Iron

Human nutritional requirement for brain function include proteins, certain types of fat, iron, zinc, copper, iodine, selenium, vitamin A, choline and folate. Iron is the most abundant transition metal within the brain, and is vital for a number of cellular processes including neurotransmitter synthesis, myelination of neurons and mitochondrial function. Theimpact of the deficiency of any nutrient on brain development is determined by the period in which the deficiency occurs, its degree and duration.[3,7] The specific influence of the deficiency of a given nutrient depends on the physiological processes in individual parts of the brain in which the nutrient participates, and is manifested as a neurological function disorder in that specific area. The blood-brain barrier provides an effective regulatory point for iron movement in the human nervous system. Ferritin moves from the plasma pool to the cerebral and spinal fluid, and from the choroid plexus it moves into and out of the brain. Magnetic resonance imaging (MRI) has been used to map iron distribution in the brains of children and adolescent.[16,17] The highest concentrations are found in the Globus pallidus, caudate nucleus, putamen and substantia nigra.

Ferritin is essential for a number of enzymes involved in neurotransmitter synthesis[3,6,7] including tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine and dopamine). Iron is related to the activity of monoamine oxidase, an enzyme critical for proper rates of degradation of these neurotransmitters. In addition, iron is a cofactor for ribonucleotide reductase, and is essential for the functioning of a number of electron transfer reactions related to both lipid metabolism and brain-energy metabolism.[7]Irondeficiency therefore affects myelinisation, monoamine neurotransmitter synthesis and hippocampus metabolism during infancy. Reductions in speed (myelinisation), changes in motor control and affect (monoamines), and memory (hippocampus) all bear witness to these influences.[2,3,6]The *hippocampus* is part of the limbic system and plays important roles in the consolidation of information from short-term *memory* to long-term *memory*, and in spatial *memory* that enables navigation. Information is initially processed and consolidated by the hippocampi before being stored in the cerebral cortex.

Impact of iron deficiency on childhood intelligence

Iron is important for normal development of the brain which is the seat of human memory. Iron deficiency during pregnancy and lactation causes irreversible damage to foetal/neonatal brain development and function, which may be manifested as arrested cognitive and social development.[2,7] The basal ganglia and hippocampus support a number of cognitive processes, including higher-order cognitive functions such as general intelligence.[18,19]

Knowledge is a familiarity, awareness, or understanding of someone or something, such as facts, information, descriptions, or skills, which is acquired through experience or education by perceiving, discovering, or learning. It is synonymous with appreciation, cognition and intelligence. It requires the storage of information (memory) in the cerebral cortex and the retrieval (recall) of same in appropriate circumstances. Children exposed to iron deficiency both in utero and in the newbornperiod will suffer irreversible mental deficiency. Iron-deficiency anaemia is common during the second and third years of life and has variably been associated with developmental and behavioural impairments, hence it can influence motor and cognitive skills and the children so affected will present with the following:[3,7]

Depressed mood
Short attention span
Loss of alertness
Loss of interest in the surrounding
Poor memory
Poor school performance

These brain related deficiets will limit the child's capacity to learn hence impaired intellect in the short- and long-term. Subsequent therapeutic correction of the serum iron will not revert the brain function to normal. A large number of children with attention deficeit hyperactivity disorder (ADHD) are known to be mentally retarded.[18] The hallmark of this condition is short attention span and lack of focus which consequently affect learning.ADHD has been associated with an imbalance in the brain level of dopamine, a neurotransmitter which requires iron for its synthesis.[18] Serum or peripheral iron in ADHD children is known to be normal but study has reported reduced brain iron in the thalamic region as measured by magnetic resonance imaging (MRI) in ADHD patients suggesting a role iron in the pathogenesis of this disease.[20,21]

A limited number of studies have been conducted to determine if iron deficiency during non-developmental periods of life are associated with changes in behaviour, cognition and brain function. Studies in adolescents who were iron deficient, but not anaemic, revealed alterations in cognitive functioning that could be attributed to iron depletion but not anaemia. When specific tests of attention were performed, iron-deficient anaemic adolescents performed less well than iron-sufficient teens but these individuals did respond to iron therapy.[17, 22]

Conclusion and recommendation

Iron-deficiency anaemia (and low serum iron) in pregnancy and childhood in developing countries is largely related to under nutrition thus making this problem a high-priority topic and highlights the key role of primary and secondary prevention. Studies have shown that iron-deficiency anaemia in pregnancy creates a significant risk of reducing foetal iron storage thus causing cerebral dysfunction to occur in utero.[3-5]Even if the iron deficiency is corrected after birth, their brain function may never be fully restored. Furthermore, the amount of iron in the mother's milk is not usually sufficient to satisfy the infant's iron needs after the first six months of exclusive breast feeding during the first year. Iron supplements for breastfeeding mothers has not produced satisfactory results once the damage has already been done. This highlights the importance of preventing iron deficiency among women during pregnancy and breastfeeding. It is also important to adopt some other preventive measures to cover infants especially during the first two years of life when brain growth is most rapid. The brain is formed from the third week of intrauterine of life; its metabolism and volume continue to increase from birth to adulthood;[23] at the age of five years a normal child attains 90 per cent of his brain growth.

The WHO estimates that more than 30 per cent of pregnant women in developing countries has iron-deficiency anaemia and one in 4 to 5 babies develop iron deficiency anaemia.[24,25] Anaemia is only a late manifestation of iron deficiency, and iron deficiency without anaemia is more widespread.[26] If subtle effects of iron deficiency in infancy lay the ground for later problems in cognitive and behavioural functioning, then a large unrecognised population of children may be at risk due to perinatal iron deficiency, a nutritional problem that can be prevented, or treated.[24-26] Frequent pregnancy disorders such as intrauterine growth restriction[27] and gestational diabetes mellitus[5,28,29] increase the risk of iron deficiency in the late foetal and early neonatal period.

In view of all these, the routine programme of iron supplementation to every pregnant woman should be undertaken with a greater level of seriousness especially in the developing world countries. There is also the general recommendation that iron should be administered to all breastfed infants after the sixth month, and to all prematurely born infants and infants born with low birth weight after the second month.[24,25]
Additionally, serial capillary haemoglobin check-ups at well-baby clinics, is recommended. In areas where hookworm infestation is rife, heath education on environmental sanitation is mandatory plus regular deworming programme partly towards preserving young brains.

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