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Effect of iron deficiency anemia on cognitive development

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ABSTRACT

Anemia is a major public health problem affecting 1.62 billion people globally. Iron deficiency anemia is the most widespread micronutrient deficiency affecting all age groups irrespective of gender, cast, creed and religion. Iron deficiency affects 20 to 50 per cent of the World's population, making it the most common nutritional deficiency. It is prevalent in most of the developing world and it is probably the only micronutrient deficiency of public health relevance in developed countries. Numerous intervention studies have been performed across the world with varying success and it is clear that in nearly all situations it is a preventable disease with preventable consequences. One such consequence is alteration in cognition that occurs in iron deficient individuals during the early parts of their life cycle. Even short term nutritional deprivation, hunger, or skipping a meal can adversely affect cognitive development and performance. Impaired cognitive function is one of the several potential outcomes of deficiencies of iron and zinc

Key Words : Anemia, Cognitive development

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Nutritional anemia is a worldwide problem, particularly in the developing countries where nearly two billion individuals are affected, with a significant proportion being constituted by children and women of child bearing age (WHO, 2001). Adequate iron nutrition in infants and children is necessary for optimal health and growth and to provide a foundation for school and lifelong learning. The costs of iron deficiency anemia are high. Children who are slow to learn may limit the ability of teachers to fulfill their tasks and hold back their classmates, they may need special schools, and they may have increased infection rates and, therefore, increase the load on the health system.

Senderowitz (1998), termed anemia, a critical health concern as it affects growth and energy level. It is a serious world wide problem especially in developing countries. World Health Organization (WHO) has estimated 27 per cent of adolescents as anemic.

Anemia is a major public health problem affecting 1.62 billion people globally. Although the prevalence of anemia is estimated at 9 per cent in countries with high development, in countries with low development the prevalence is 43 per cent (Mc lean *et al.*, 2009). Children and women of reproductive age are most at risk, with global anemia prevalence estimates of 47 per cent in children younger than 5 years, 42 per cent in pregnant women, and 30 per cent in non-pregnant women aged 15–49 years, and with Africa and Asia accounting for more than 85 per cent of the absolute anemia burden in high risk groups. Anemia is estimated to contribute to more than 1,15,000 maternal deaths and 5,91,000 peri-natal deaths globally per year (Ezzati *et al.*, 2004). The consequences of morbidity associated with chronic anemia extend to loss of productivity from impaired work capacity, cognitive impairment, and increased susceptibility to infection (Hass and Brownlie, 2001), which also exerts a substantial economic burden (Horton and Ross, 2003).

Determinants of the prevalence and distribution of anemia

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in a population involve a complex interplay of political, ecological, social, and biological factors. At the country level, anemia prevalence is inversely correlated with economic development children and women of reproductive age because of their physiological vulnerability are at high risk, followed by elderly people, and men (Mc Lean *et al.*, 2009).

Iron deficiency anemia occurs when iron stores are exhausted and the supply of iron to the tissues is compromised. IDA is a severe stage of iron deficiency in which hemoglobin (or hemocrit) falls below the above cutoffs. In particular, iron deficiency anemia leads to weakness, poor physical growth, and a compromised immune system decreasing the ability to fight infections and increasing morbidity and is also thought to impair cognitive performance and delay psychomotor development. Recent macroeconomic estimates suggest that the average impact of iron deficiency anemia, through both physical and cognitive channels, could be as large as 4 per cent of GDP in less developed countries (Horton and Ross, 2003). Through the impact on schooling, anemia could also be central to understanding the international transmission of poverty.

Consequently, assessments of anemia as well as interventions and policies to reduce anemia largely focus on women and children. Adolescents are also a key group, with adolescent girls being targeted for intervention before the onset of childbearing (Micronutrient Initiative, 2009).

In children iron deficiency develops slowly and produces few acute symptoms. As the deficiency worsens children become pale and weak, eat less and tire easily. They gain weight poorly, have frequent respiratory and intestinal functions, and may develop pica. The most worrying association is that between iron deficiency and impaired development in behavior, cognition and psychomotor skills. Over the past three decades many studies have confirmed this relation, but whether iron deficiency is the sole cause of these deficits remains unclear.

Anemia is socially associated with education, wealth, occupation (*e.g.*, agricultural workers), and residence. In most settings, anemia is a marker of socioeconomic disadvantage, with the poorest and least educated being at greatest risk of exposure to risk factors for anemia and other micronutrient deficiencies. The pooled analysis showed that the risk of anemia among women living in the lowest wealth quintiles was 25 per cent higher than among those in the highest wealth quintile (Balarajan *et al.*, 2011). Women with no education were more likely to be anemic than were those with greater than secondary education. Patterning of anemia by socioeconomic status was also noted for children. A child living in a household in the lowest wealth quintile was 21per cent more likely to be anemic than were those in the highest wealth quintile (Balarajan *et al.*, 2011). Risk of anemia was also raised in children whose mothers had no education. Conditional on demographic and socioeconomic factors, mother's anemia status was among the strongest predictors of anemia in children.

What are the factors responsible for causing anemia?

Socio-cultural:

Due to the patriarchal nature of our society, women are discriminated against from birth. The discrimination against girls results in an attitude of neglect towards them and they receive inadequate nutrition right from childhood. Nutrition deficiency such as protein, vitamin C and iron leads to anemia among most girls and women. After marriage, a woman's status in the family and society is determined by her reproductive functions and that too on the number of male children she bears.

The girl child does not receive adequate breast milk or food:

Many a time, the girl child is not only breastfed for a less duration but food supplementation to her is also delayed.

During adolescence, the increased requirement of iron, is not met with:

In the adolescent phase due to menstruation, the requirement of iron increases. Every month about 40 ml. blood is lost with approximately 0.6 mg of iron. This increased requirement for iron is not met due to discriminatory social beliefs and food restrictions.

Women do not get adequate food and rest as comparised to the work they do:

Usually women perform multiple roles which include work in and out of the house since childhood. In comparison to the work they do, they not get adequate nutrition and rest.

Food related taboos:

Girls and women are expected to follow numerous social and religious rituals and food taboos related to menstruation, pregnancy and lactation that hinder their nutritional intake. For example, it is not uncommon for women to observe a fast two to three days in a week without any change in their workload.

Inadequate information about food and cooking methods:

Most women do not have adequate information about the nutritive quality of food. Moreover, time and energy is required to pluck, sort out, cut and wash leafy vegetables the quantity of which decreases on cooking. Amongst the numerous tasks performed by women, this becomes an additional burden due to which leafy vegetables are avoided.

No decision making power:

Most girls are not groomed to make decisions regarding their life, health, education or marriage. This holds true even in case of food allocation and consumption.

Lack of self-esteem:

The lack of self esteem makes women offer their husbands the best of everything available in the household including food. It is believed that if a woman, who cooks food, eats first, does not have a prosperous household. She is supposed to eat last, never grumble about getting less or not eating rich diet.

Economic reasons:

Due to poverty, women are forced to work hard for long hours to supplement household income. Lack of opportunities to develop professional skills and competencies, makes them take up jobs that are less paying and harmful to health. Due to non existence of appropriate laws especially a law enforcing equal wages for equal work, women are paid less for the same amount of work as compared to their male counterparts. Women continue to perform their household, productive and reproductive roles without adequate nutrition which results in anemia.

Poor access to health care:

Besides food intake, conditions of general health/ill-health also influence women's nutrition to a great extent. Illness episodes, severity and duration of illness, treatment received and care during and after the illness affect women's nutrition. Recovery from illness is a longer process for anemic women. Thus, anemia and illness interplay in a vicious cycle.

Poor policies and programmes:

Most of the countries in the South Asian region do not have comprehensive national programmes for the prevention and control of iron deficiency anemia. The few programmes that exist lack an integrated approach and are gender insensitive. These programmes made very little impact because of they did not take into account the socio-economic and political reasons of anemia among women. For example, most of the programmes address nutrition during the first six years of life, and then skip directly to pregnancy and lactation. Adolescence, which is the period of additional nutritional requirement, is not addressed through these programmes. Very little space is available to create awareness on the importance of understanding women's nutritional needs throughout various stages of her life, and to ensure that women eat the food that reaches the household.

Agriculture:

The green revolution (increasing crop production by improving soil fertility, pest control and increasing the use of machines/equipment) helped in increasing food grain production, from 50.82 million tonnes during 1950–1951, to 198.96 million tonnes in 1996–1997. Despite having achieved self-sufficiency in the production of cereal and grain, consumption is still inadequate, and food security at the household level is still a concern. With a significant shift in the cropping pattern from food crops such as pulses and coarse grains (which are the traditional staple food of poor communities) to export- oriented cash crops, the food and nutritional intake of people stands hampered. Even the income from sale of cash crops does not ensure women's food security because women have no control over how the money is spent.

As a result of trade liberalization policies, cereal exports have increased and food subsidies have been cut further. Prices of basic staples food items, such as wheat and rice, have increased so much that they are now higher in India than on the international market.

Due to inefficacy of the public distribution system (PDS), poor people have no choice but to buy from the open market where prices are higher. Women who are the poorest of the poor do not afford to eat enough themselves. Even the food processing industry which has traditionally been 100 per cent women- centered cottage in terms of income and employment has become institutionalized. Private business in the food processing sector is introducing expensive junk food in the market that is not necessarily nutritious

Kriplani (2006) stated that in India, more than 70 per cent of women are affected with iron deficiency anemia (IDA), among them, every fifth women is affected severely.

Jondhale *et al.* (2001) reported a prevalence of anemia as 14 per cent in adolescent girls where the household income was more than Rs. 5000 per month and 26 per cent where the household income was less than Rs. 5000 per month.

Basu *et al.* (2004) conducted a study to assess the prevalence of anemia among school going adolescents of Chandigarh and found that prevalence of anemia is higher among girls (23.9%) as compared to boys (7.7%). Anemia was observed more in rural (25.4%) as compared to urban (14.2%) adolescents. A consistent finding in different countries is that severe, chronic iron deficiency in infancy identifies children with poor cognitive function and lower scores in school achievement tests, suggesting that irreversible abnormalities result from a deficiency at a critical period of growth and differentiation of the brain.

In India, this silent emergency *i.e.* iron deficiency anemia is rampant among women belonging to reproductive age group (15- 49 years), children (6-35 months) and low socio- economic strata of the population. Overall, 72.7 per cent of children up to the age 3 years in urban areas and 81.2 percent in rural areas are anemic. While analyzing the data for states with anemia level of 70 per cent among children, it was found that, except for Punjab, all other states had more than 50 per cent prevalence of anemia among pregnant women. This again reiterates the strong relationship between anemia levels of mothers and children. Also, the overall prevalence has increased from 74.2 per cnt (1998-99) to 79.2 per cent (2005-06). Nagaland has the lowest prevalence (44.3%), Goa has next (49.3%) followed by Mizoram (51.7%). Bihar had the highest prevalence (87.6%) followed closely by Rajasthan (85.1%) and Karnataka (82.7%). Moderate and severe anemia is seen even among the educated families both in urban and rural areas. There are inter- state differences in prevalence of anemia that are perhaps attributable partly to differences in dietary intake and partly to access to health (Govt. of India, 2008).

According to a provisional data of the 2005- 06, National Family Health Survey (NFHS- 3), more than 82 per cent children in Haryana are anemic whereas, as per District Level Health Survey (DLHS) 2002-04, prevalence of anemia in adolescent girls is very high (72.6%) in India, with prevalence of severe anemia among them much higher (21.1%) than that in preschool children (2.1%). Particularly the girls entering in their reproductive years with poor iron status may transfer this deficiency to their off springs again increasing the risk of low birth weight, preterm delivery and still births. There are so many factors causing anemia, but inadequate intake of iron from food sources is one of the main reasons especially in case of adolescent girls in order to compensate blood losses during menstruation and only because of that an additional requirement of iron increased up to 15 per cent (*www.whosea.org*).

Iron deficiency can make feel tired, irritable and less able to concentrate. In children, it can affect behavior and may cause mental disorders (www.britishnutrition.org.uk), work performance, learning capacity and concentration of the child may be perturbed due to anemia. Iron deficiency in children is associated with lower score on tests and development, and with impaired learning and school achievements. Over the past decade and a half, the relationship between iron deficiency and cognitive performance has received increased attention and confirmation. School achievements and performance in mental educational tasks is poorer among iron deficient anemic children. Chronic iron deficiency anemia is likely to produce increasingly unfavourable educational outcomes that will require nutritional treatment and additional education to correct.

Most of the symptoms of iron deficiency are a result of the associated anemia, and may include fatigue, rapid heart rate, palpitations and rapid breathing on exertion. In iron deficiency anemia, the reduced hemoglobin content of delivery to active tissues. Decreased myoglobin levels in muscle cells limit the amount of oxygen that can be delivered to mitochondria for oxidative metabolism. Iron depletion also decreases the oxidative capacity of muscle by diminishing the mitochondrial content of cytochromes and other iron dependent enzymes required for electron transport and ATP synthesis.

Lactic acid production is also increased in iron deficiency. The ability to maintain a normal body temperature on exposure to cold is also impaired in iron deficient individuals. Severe iron deficiency anemia may result in brittle and spoon shaped nails, sores at the corners of the mouth, taste bud atrophy, and a sore tongue.

Infants and young children are the most adversely affected by iron deficiency because they are growing and developing at such a fast rate. If iron deficiency is not corrected, it leads to anemia and is associated with impaired development of mental and physical coordination skills. In older children, iron deficiency leads to impaired school achievement.

The etiology of anemia is multifactorial; however, from a public health perspective, iron deficiency is believed to be the most important causal factor. The WHO estimates that roughly 50 per cent of anemia prevalence can be attributed to iron deficiency. Most observational studies in children have found associations between iron deficiency anemia and poor cognitive and motor development, and behavioral problems. Iron is the component in many proteins, including enzymes and hemoglobin, the latter being important for the transport of oxygen to tissues throughout the day (National Academies of Sciences, 2002). Iron Deficiency Anemia (IDA) –that is low levels of Hb in combination with abnormal levels of other iron indicators such as transferrin saturation (iron stores)-can lead to weakness, poor physical growth, increased morbidity, and delayed psychomotor development. In particular, animal studies suggest that iron deficiency early in life could inhibit the function of neurotransmitters, comprising later brain functions. Many enzymes in neural tissue require iron for normal function. The cytochromes involved in energy production, for example, predominantly are heme proteins.

Heme is an iron containing compound found in a number of biologically important molecules. Hemoglobin and myoglobin are heme containing proteins that are involved in the transport and storage of oxygen. Hemoglobin is the primary protein found in red blood cells and represents about two-thirds of the body's iron. The vital role of hemoglobin in transporting oxygen from the lungs to the rest of the body is derived from its unique ability to acquire oxygen rapidly during the short time it spends in contact with the lungs and to release oxygen as needed during its circulation through the tissues. Myoglobin functions in the transport and short term storage of oxygen in muscle cells, helping to match the supply of oxygen to the demand of working muscles.

Iron's role in congnition:

Cognition, or one's ability to perceive, think and remember, is influenced by many factors, one of which is nutrition (Kretchmer, 1995). Protein–energy malnutrition, a multiple nutrient deficiency syndrome, is associated with a variety of cognitive and behavioral deficits. Among children, protein-energy malnutrition impacts mental development and cognition. It also reduces children's interaction with the environment which, in turn, can lead to problems with attention, inactivity and unresponsiveness. Each of these behaviors may compromise children's ability to learn. Among older adults, malnutrition may lead to cognitive deficits and reduce their ability to function independently. Even short term nutritional deprivation, hunger, or skipping a meal can adversely affect cognitive development and performance. Impaired cognitive function is one of the several potential outcomes of deficiencies of iron and zinc (Pollitt, 1993).

Brain development does not stop after birth; it continues to develop throughout childhood until adulthood. Different lobes of the brain (including their functions) develop at different ages the (pre) frontal lobe for instance continues to develop during adolescence. Through all these phases nutrition may influence the course of brain development, for example-docosahexaenoic acid (DHA) has a role in myelination. Iron has also been suggested to play a role in the myelination process as well as in neurotransmitter function.

There is now strong supporting biological evidence from laboratory studies of animals that iron deficiency anemia harms brain development. In the last 10 years, two central nervous system mechanisms have been claimed to cause the behavioral changes associated with iron deficiency:

– The first is that iron deficiency impairs the myelination (myelin is a soft, fatty material that forms a thick cover around nerve fibers) of nerve cells.
– The second is that it affects neurotransmitter function (the transmission of nerve impulses). The metabolism of neurotransmitters, including dopamine, is clearly altered. These changes in central nervous system appear to be readily reversible and could be related to the changes in attention observed in children suffering from iron deficiency anemia and, therefore, alterations in dopamine metabolism. It is likely that the effects of iron deficiency on dopamine metabolism are independent of the myelination effects.

Furthermore, these two effects may be age dependent and relate to the maturity of the brain, with the effects on myelination occurring during the latter part of the spurt in brain growth during infancy. Whether this explains the lack of effect of iron supplements on the poorer mental and physical coordination development test scores of iron deficient anemic infants remains to be determined.

Since the initial studies of Oski and Honig (1993), most research on the cognitive effects of iron deficiency has focused on infants and very young children (toddlers). Several studies have shown that iron deficiency causes changes in behavior and lowers development test scores in infancy. Animal models have revealed several mechanisms by which iron deficiency may affect cognition; these include changes in brain iron content and distribution, and in neurotransmitter function. Body iron stores, such as central nervous system iron, decrease before red blood cell production is affected by iron deficiency. Decreased brain iron stores may impair the activity of iron-dependent enzymes necessary for the synthesis, function and degradation of neurotransmitters such as dopamine, serotonin, and nor- adrenaline

Findings from both experimental animal and human studies provide evidence for the role of iron in cognitive function. In laboratory animals, iron deficiency anemia reduces iron in specific areas of the brain, which in turn impairs myelination of nerve cells and neurotransmitters, especially dopamine (Sandstead, 2000). These changes could lead to alterations in the maturation and function of variety of aspects of the central nervous system involved in specific behaviors. Iron deficiency in experimental animals could also affect cognitive behaviors by reducing animals' attentiveness and responsiveness to environmental stimuli. This, in turn, could lead to fewer learning experiences and less ability to obtain information (National Cattlemen's Beef Association, 1999).

Similarly, among adolescents, iron deficiency anemia is associated with poor academic performance and iron supplementation improves test scores related to specific components of cognition. A double-blind, placebo-controlled trial involving 73 adolescent girls with mild iron deficiency found that supplementation with oral ferrous sulphate (650 mg twice daily or 260 mg elemental iron) for 8 weeks improved verbal learning and memory, both of which are important academic performance (Bruner *et al.*, 1996).

It is well recognized that nutritional iron deficiency (NID) is the most prevalent nutritional deficiency in the world. It can affect more than 400 million individuals (WHO, 2001) and is indeed most prevalent in infants and young children. The importance of iron is systemic cellular biochemistry, where it is utilized in the synthesis of DNA and proteins and is involved as cofactor for numerous enzymes, structural protein and physiological responses is well recognized.

The prevention and control of iron deficiency anemia in infants and young children should, therefore, be a priority on national nutrition and health agendas not only to improve child survival, but also to realize children's full potential and to maximize their contribution to national development. There is a need for data on the prevalence of iron deficiency anemia at both global and the national level, but this does not lessen the urgent need to address iron deficiency anemia in infants and young children and its impact on human potential. Advocacy at all levels is needed to ensure that this problem is addressed.

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