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REVIEW ARTICLE

Cognitive Development in Anemic Children

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ABSTRACT

Worldwide, iron deficiency is prevalent single nutrient disorder. *Ayurveda* too recognises it as a specific clinical entity, *Pandu*. Infants and women are the most vulnerable and at more risk as compared to other age group. One of the most worrying upshots of iron deficiency in children is the variation of behavior and cognitive performance. In this review, the aim is to summarize studies in human, especially children, looking for evidence of a causal relationship between iron status and cognition and behaviour. Most co-relational studies have found associations between iron deficiency anemia and poor cognitive and motor development, and behavioural problems. Few preventive trials had design problems, or produced no or questionable benefits only. This finding provides evidence that in some situations, cognitive shortfalls are not always permanent. It is concluded that during infancy, poor supply of iron results in iron-deficiency anemia and associated with stunted growth, and decreased psychomotor development. Iron-deficiency anemia in infancy has been shown to have a persistent negative influence on the attainment in tests of psychomotor development.

Key words: Anemia, Cognitive performance, Impaired growth, Motor development, *Pandu*, Psychomotor development

INTRODUCTION

Anemia is a global public health problem with major consequences for human health and has affected more than two billion people worldwide. [1] Anemia is the lack of red blood corpuscles (RBCs) and hemoglobin in the blood, and is defined as a qualitative or quantitative deficiency of hemoglobin. Though every age group is susceptible to affliction with anemia, it is more common in small children and pregnant women because of iron deficient diet intake. It has been estimated that 50% of women of reproductive age are affected with Iron Deficiency Anemia (IDA).[2] Among the affected population, children under five years is one of the most vulnerable groups, especially those in the first two years of life. [3] As per the World Health Organization (WHO) report, iron deficiency is most common among groups of low socio-economic status.

Anemia is well correlated with the disease '*Pandu'* described in *Ayurvedic* system of medicine. They have described '*Alp-Rakta*' (less blood) as a symptom in *Pandu Roga* and *Shithilendriya* (less strength of sensory and motor sytem) as a consequence. [4, 5] Cognition disorder could be taken in broad term of *Shithilendriya*. Early growth and development of a child's life is fundamentally important and are the foundation that shapes children's future health, happiness, growth, development and learning achievement at school, in the family and community, and in fact the whole life across the life span. Cognitive development is the emergence of the ability to think and understand. [6] Jean Piaget was a major force in the establishment of this field, forming his "theory of cognitive development". Piaget proposed four stages of cognitive development: the sensorimotor, preoperational, concrete operational and formal operational period. [7]

Significant differences in mental development scores have been observed at hemoglobin concentrations less than 10.5 g/dl. Children who are deficient in iron during infancy, even though they have been provided treatment for the condition at that time, after ten years, are found to score significantly lower than controls on the measures of mental functioning. [8] Epidemiological evidence has shown that anemia in children impaired psychomotor development and immune competence, led to poor cognitive and physical development, caused mental retardation, and increased their mortality and morbidity. [9]

Iron deficiency is the most common single nutrient disorder in the world, [9] and infants are at particular risk due to their rapid growth and limited dietary sources of iron. [10] In iron-deficient children, striking behavioural changes are observed, such as reduced attention span, reduced emotional responsiveness and low scores on tests of intelligence. [11] The reported prevalence of IDA in young children varies in different populations, depending on the case

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definition used, with estimates ranging from 10% in western societies, to around 50% in less developed societies. [12] Most researches on infants and young children are consistent with a negative effect of IDA [13] on cognitive and behavioral development. [14] Effects of early stunting on cognitive deficits can persist throughout later life, [15] and successive generations. [16]

Iron deficiency is a very common nutritional disorder worldwide and is known to affect approximately one third of the global population. While its incidence in affluent countries is low, the incidence of IDA in India is very high. According to National Family Health Survey (NFHS) III data, the incidence of anemia in urban children is 71%, rural 84%, and overall is 79%. [17] Nutritional iron deficiency is the most common cause of anemia in India. [18]

Stunted children of India, performed poorly and had much lower scores than adequately nourished children on cognitive tests. [19] In addition, in children from developing countries such as Ecuador, [20] Vietnam, [21] Brazil, [22] Malaysia, [23] and Cambodia, [24] stunting was a significant predictor of lower cognitive test scores.

In general, the severity of anemia is differentiated by the severity of the reduction in hemoglobin level. [25] Severe anemia usually comprises a small proportion of the cases in children, but may cause a large proportion of the severe morbidity and mortality. [26] A world-wide report also showed that moderate-to-severe anemia increases the risk of mortality in the vulnerable population.[27] Approximately 20% to 25% of all infants in the world have IDA, and many more have iron deficiency without anemia. [28]

Aim of this study

If subtle effects of iron deficiency in infancy lay the ground for later problems in cognitive and behavioural functioning, then a large, unrecognized population of children could be at risk owing to iron deficiency, a nutritional problem that needs to be prevented and treated. The aim of the study is to summarize scientific studies in human, especially children, looking for evidence for the correlation of IDA and poor cognitive and behavioural development, as well as relation between iron status and cognition.

MATERIALS AND METHODS

A comprehensive study was done on anemia and its causal relationship with cognition and behavior, especially in children. For this, a good number of relevant research papers and articles were reviewed, both from print and online scientific electronic databases as PubMed, Google scholar etc. Descriptions were also collected from some books and standard *Ayurvedic* literatures (*Samhitas*).

REVIEW

Most correlational studies have found associations between IDA and poor cognitive and motor development and behavioral problems. For instance, 5% of poor black and latino infants and toddlers have IDA, and iron deficiency (with or without anemia) affects 18% and 12% of poor and non-poor Mexican American infants, respectively. [29] Studies consistently indicate that children anemic in infancy continue to have poorer cognition, school achievement, and more behaviour problems into middle childhood. It therefore remains uncertain whether the poor development of iron-deficient infants is due to poor social backgrounds or irreversible damage, and whether is remediable with iron treatment. Earlier, there have been a considerable number of studies on the relationship between iron status and cognition, but the topic remains controversial. [30] Many professionals are lobbying to promote fortification or supplementation programs, claiming conclusive evidence of a causal relationship between iron deficiency and poor cognitive development; whereas others consider that there is no clear evidence. [31]

Several factors found to be associated with both anemia and poor cognitive development are low socioeconomic status; [32] poverty; [33] lack of stimulation in the home; [34] poor maternal education, [34 & 35] and intelligence quotient (IQ); [36] maternal depression; [34] more absent fathers; low birth weight and early weaning; [36] parasitic infection; [37] and undernutrition. It is highly unlikely that all of these factors are controlled for in one study, and there are probably many other confounding factors.

Beginning from as early as 1919, many investigators found significant associations between hemoglobin concentrations and measures of cognitive development. [38 & 39] In trials concerning children, two year old, in six of seven studies with non-anemic and anemic children, [35, 40] the anemic groups had significantly scored lower on the mental development index (MDI) of the Bayley Scales. There were only eight non-anemic children in the seventh study. [41] Four of the studies also showed differences in the psychomotor development index (PDI). [35, 42] Most importantly, most of the studies found that formerly anemic children continued to be at a developmental disadvantage at one or more of the follow-up assessments.

Specific cognitive functions were assessed in only a few studies. In Costa Rica and Chile, [34, 36, 43] children were given a comprehensive battery of tests at five year of age. In both studies, the formerly anemic children had deficits, which were not identical, across a wide range of functions. Preschool skills, fine and gross motor skills and visual-motor integration were affected in both studies, whereas language and global IQ were affected in the Chilean sample. [34] Children in Costa Rica were reassessed between ages 11 and 14 year for an even wider range of functions. [43] In conclusion, longitudinal studies indicate consistently that children who were anemic in early childhood continue to have poor cognitive and motor development and school achievement into middle childhood. [43] Of the five longer-term studies that had non-anemic

groups, the treated anemic group failed to catch upto the non-anemic group in scores on the Bayley test in three studies. [40, 42, 44]

There were four studies from India, [45] and in each the children were randomly assigned to treatment or control, regardless of hemoglobin level. However, the iron-treated group was significantly better than the control group at the end in the second study. At the end of third study, the treated groups had higher scores than the nontreated groups. Only the fourth study reported difference between the groups in change of scores, but they restricted the analysis to anemic children only, thus breaking the paired randomized design. [46]

Sally Grantham-McGregor and Cornelius Ani, 2001, reviewed that in several but not all studies, anemic children have failed to catch up to non-anemic children with iron treatment. Anemic older children also usually had poorer cognition and school achievement than did non-anemic children. They usually catch up in cognition with repeated testing and treatment but not in school achievement. There are more Randomized Control Trial with this age group, and it has clearly been shown in four studies that children benefited from iron treatment while three others show that a treatment benefit was highly likely. At present, the evidence for a beneficial effect of iron treatment on cognition in anemic older children is reasonably convincing, but it would be helpful to run one or two more rigorous RCT with detailed reporting of the results. [46]

John L. Beard, *et al.* 2004, conducted a prospective, randomized, controlled, intervention trial in South Africa among three groups of mothers: non-anemic, controls and anemic mothers of full-term normal birth weight babies, and were followed from ten weeks to nine months postpartum. Maternal hematologic and iron status; socioeconomic, cognitive, and emotional status; infant and mother interaction; and the development of the infants were assessed. The study demonstrated that there is a strong relation between iron status and depression, stress, and cognitive functioning in poor African mothers during the postpartum period. There are likely ramifications of this poorer "functioning" on mother-child interactions and infant development. [47]

Dawd Gashu, *et al*. 2016, studied that, no significant difference was found between cognitive scores of iron deficient and normal children. In addition, none of the iron biomarkers was found to have significant association with the cognitive performance of children. Iron may have had weak effects here because most of the children in that study were iron sufficient. Compared to non-anemic children, anemic children however had significantly lower cognitive scores for the verbal reasoning test. Nevertheless, in addition to poor iron status, anemia is caused by several socioeconomic conditions and dietary factors too. [48] Thus, the difference in cognitive performance of the study anemic and non-anemic preschool children may not be attributed to iron status alone. [49]

Betsy Lozoff, *et al.* 2000, concluded that children who had severe, chronic iron deficiency in infancy continue at behavioral and developmental disadvantage relative to peers. The statistical significance of different follow-up studies in Israel, Chile, and France found that four- to eight-year-old children who had been anemic as infants or toddlers, tested lower than peers even several years after the iron treatment. [50] Ten years after treatment, children who had moderate IDA as infants continued to test lower in mental and motor functioning, as did the children with higher hemoglobin levels that still had some biochemical evidence of iron deficiency after iron therapy in infancy. [51]

In Indian Journal of Clinical Biochemistry, 2005, Batra Jyoti and Sood Archana stated that, studies have indicated that anemic children of less than two years have failed to catch up with non-anemic children even after iron supplementation. [52] The anemic children of more than two years also usually had poorer cognition and school achievements as compared to non-anemic ones. They usually catch up in cognition with repeated testing and treatment, but not in school achievement. [53] Most of the co-relational and experimental studies done earlier confirmed the hypothesis that iron deficiency of mild to moderate nature has an adverse effect on congnitive development. [54] Therefore, it may be logical to suggest that impairment of higher mental functions like cognition and learning in humans, [55] may be linked to changes in neurotransmitter receptors and consequent signal transduction process in the nervous system. [56] It is thus inferred that iron deficiency is usually associated with many psychosocial, economic and biomedical disadvantages. [57]

R. Colin Carter, *et al*. 2010, examined the effects of IDA on specific domains of infant cognitive function, and the role of IDA-related socio-emotional deficits in mediating and/or moderating these effects. Infants were recruited during routine nine month visits to a clinic. Those data indicate poorer object permanence and short-term memory encoding and/or retrieval in such infants. These cognitive effects were attributable, in part, to IDA related deficits in socio-emotional function. Children with poor socio-emotional performance seem to be more vulnerable to the effects of IDA on cognitive function. [58]

Betsy Lozoff, *et al.* 2006, stated that in human infants with chronic, severe iron deficiency, delayed or mistimed sensory input, together with cognitive, motor, and affective changes, may adversely affect the infant's interactions with the physical and social environment. [59] Children who had IDA in infancy continue to perform less well than the peers who had good iron status in infancy. They have done worse on tests of overall mental, motor, and social/emotional functioning and on specific neuro-cognitive tests at preschool, school age, and adolescence. [60]

The long-term effects of IDA have been addressed by two recently described follow-up studies in five-year-old Costa Rican [61] and Chilean [62] children, who had been well characterized as

infants in both iron status environmental variables and psychomotor development. At five years of age, an evaluation with a comprehensive set of psychometric tests showed that those children who had presented with IDA in infancy, showed lower scores on many of these tests when compared to those children who had higher hemoglobin during their infancy.

DISCUSSION

Worldwide, iron deficiency is a very common nutritional disorder and is known to affect almost one third of the global population. Studies have reported lower performance scores among infants who had been anemic compared to non-anemic infants. A treasure of clinical, biochemical and neuropathological research shows that iron deficiency can negatively effect on learning and this can occur even with normal haemoglobin levels against the astound impact of socioeconomic factors. Tomas Walter, 2003 concluded, behavioral studies have consistently shown that IDA has adverse effects. Even ancient *Ayurvedic* literatures have clearly recognised this clinical entity and its impacts on human health. All such studies viewed together, suggest new, promising directions for understanding more specific central nervous system mechanisms by which IDA could alter infant behavior and development. Evidence is strong that in many underdeveloped countries iron deficiency is the main cause of anemia, and supplementation under trial conditions may cover up some defects of iron deficiency, but not all. IDA results in tissue iron deficiency as well as devaluation in the circulating haemoglobin, and causes the most severe functional accountability. Children who had severe, chronic iron deficiency in infancy scored lower on measures of mental and motor functioning.

CONCLUSION

In children, iron deficiency anaemia (*Pandu Roga*) has been associated with psychomotor and cognitive deformity, poor school performance and mental adjournment. It is also concluded that iron deficiency is usually associated with many economic, biomedical and psychosocial disadvantages. Children who have IDA in infancy are at risk for long-lasting developmental detriment as compared with their peers with better iron status.

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