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SYMPOSIUM ON NUTRITIONAL ANEMIA-II

# Developmental and Neurophysiologic Deficits in Iron Deficiency in Children

**Nishi Madan · Usha Rusia · Meera Sikka · Satendra Sharma · Nilima Shankar**

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**Abstract**
*Introduction* Several studies in animals and humans have clearly demonstrated the effect of ID on development, cognition, behavior and neurophysiology. The effect of ID have been shown: on brain metabolism, neurotransmitter function, and myelination. Changes in brain iron content caused by early ID in animals are not reversible by iron therapy, inspite of correction of anemia and other tissue deficits and result in changes in behavior which continue into adulthood. ID has repercussions in the perinatal period, infancy and childhood. Some effects are irreversible while other defects may be corrected: timing of ID in a child may be critical.
*Developmental Deficits* Children (6–23 months) with moderate to severe anemia (ID) or chronic anemia (>3 months) had lower mental and psychomotor development scores than the nonanemic, and except for some continued to have lower scores in spite of iron therapy for 3 months although anemia was corrected. The deficits persisted on re-evaluation at 5, 11–14, and at 19 years.
*Scholastic Achievement* Scholastic achievement is lower and ID children are twice more likely to have problems with mathematics. Ten year follow-up indicated special educational assistance was required for initially anemic children. ID affects WICS items of information, comprehension and verbal performance and full scale IQ. EEG power spectrum had a slower activity suggesting developmental lag compared to iron sufficient children. Treatment with iron improved IQ scores significantly; other studies found differential effects: improvement in cognition and mental scores in older but not in younger children. IQ levels are affected by ID: IQ at 4 years may be predicted by hemoglobin at 5 and 36 months.
*Neurophysiological Deficits* Abnormal Evoked Response Potentials (ERPs):ABRs and VEPs are seen in ID, which persist in children who were anemic in infancy on retesting at 4 years. Differences have been consistently found in ID infants and in older children. Iron supplementation may significantly reduce latencies of some ERPs. ID affects newborn temperament, ERPs and recognition memory. Iron supplementation in infants (<1,301 g) improved neurocognitive and psychomotor development by 5.3 years (median age). Preventive iron supplementation in well nourished infants also show a positive effect on motor development. The changes are usually subtle, however, with prevalence of anemia of 79.2% in children 6–35 months and 57.9% in pregnant women (NFHS-3, 2005–06), the adverse effects of cognitive, development and behavioral defects should not be underestimated.

**Keywords** Iron deficiency · Evoked Response Potentials (ABR, VEP) · Neurophysiologic effect · Developmental defects

N. Madan was formerly Professor and Head of the Department of Pathology, University College of Medical Sciences & Guru Tegh Bahadur Hospital

U. Rusia · M. Sikka · S. Sharma
Department of Pathology,
University College of Medical Sciences & Guru Tegh Bahadur Hospital,
New Delhi 110092, India

N. Shankar
Department of Physiology,
University College of Medical Sciences & Guru Tegh Bahadur Hospital,
New Delhi 110092, India

N. Madan (✉)
W-131 (Ground Floor) Greater Kailash Part -1,
New Delhi 110048, India
e-mail: drnishimadan@gmail.com

## Introduction

The effect of iron deficiency (ID) on producing anemia and, in turn, its effects on the body are well known. However,

the role of ID on other organ systems, particularly on the developmental and neurological aspects, is less appreciated and also difficult to measure. The consequences of ID are probably under estimated.

## Consequences of ID

ID disrupts several pathways at the cellular level and results in changes in several tissues/organs besides varying degrees of anemia. There are several non-neurologic and neurologic sequalae.

### Neurological Sequelae of ID in Children

Interesting facts have emerged with respect to the relationship of iron to brain and its functions; ID causes neurophysiological and developmental deficits in infants, children, adolescents, which, may continue into adulthood [1].

There is evidence of reduced motor development, coordination and behavioral effects. In infants and children, there is evidence of impaired motor development and coordination; impaired language development and scholastic achievements; psychological and behavioral effects (inattention, fatigue, insecurity, etc.). In addition, there is decreased physical activity in iron deficient children [1].

## Brain and Iron

Brain contains higher concentration of iron than any other metal. In rats, iron is highly localized in the dopaminergic-peptidergic regions—globus pallidus, substantia nigra, red nucleus and accumbens. In some regions the concentration of iron is higher than that found in the liver, the site of iron metabolism [2].

In the brain, iron is an important component of enzyme systems required for DNA synthesis, respiratory chain, neurotransmitter synthesis and lipid metabolism. It is essential for a number of enzymes involved in neurotransmitter synthesis including tryptophan hydroxylase (serotonin), tyrosine hydroxylase (norepinephrine) and dopamine [3].

A high post-natal iron content is essential for neuronal differentiation, myelin lipid and receptor formation. Seventy percent of brain iron is associated with myelin. It has been observed that white matter in rat pups is markedly reduced with ID at 21 days and is even more marked if ID persists [4].

ID affects metabolism, myelination and neurotransmitter function with alterations in gene and protein profiles [5]. ID has a direct effect on myelin with decrease in myelin lipids and proteins; the number of oligodendrocytes, transferrin and transferrin mRNA are also reduced. Dopamine transporters are altered and there is evidence indicating that all monoamine transporters are also affected. In ID there is specific damage to nigostriatal neurons, which results in fine motor, gross motor, motor sequencing and sensory deficits in rats [5].

Alterations in neurotransmitters in ID in animals have been observed to be reversible or irreversible following iron therapy for correction of the deficiency. These alterations have been associated with changes in behavior (GABA) [6], decreased motor activity and learning (dopamine) [2, 7], impaired neurodevelopment or increased drowsiness, decreased attention and learning (serotonin) [8].

ID interferes with the neurotransmission in the auditory pathway and other pathways through modulating neurotransmitter synthesis [2, 7]/function, failure of myelin production, failure of generation of oligodendrocytes from precursors and interruption of oligodendrocyte maturation.

There is, however, stringent regulation of availability of iron in the brain, although there is a high iron requirement of brain, there is also a high susceptibility of brain to iron generated peroxidative damage.

## Developmental and Neurophysiologic Deficits in ID

An interesting and disturbing observation has been that there is increased susceptibility to ID during periods of tissue growth and differentiation [9]. Effect of ID has been studied extensively in animals and in the last few decades on infants, children and young adults. The possible effects on the developing brains in infants and children are extrapolated from animal models. Experimental and long-term studies on iron deficient infants indicate that this damage may not be corrected following supplementation with iron.

### Animal Studies: ID

Brain iron is present from gestation to early adulthood and very young animals are highly sensitive to ID compared to adult animals. Iron deficient rats at 21 days of age of gestation when followed-up do not normalize their brain iron content even after long-term treatment with iron. ID persists into adulthood after treatment with iron for a period of 1–3 wks [4, 5].

There is marked reduction of ferritin and total non-heme iron content of brain in rats and occurs only if ID occurs during early life when the brain is still rapidly growing. Once established, this marked reduction persists despite iron therapy, although anemia and other tissue defects are corrected [4, 5].

Also, ID for a brief period in young rats is associated with reduced brain iron and decrease in number of D1 and D2

receptors (for dopamine) of brain striatum, which, consequently produce changes in behavior. Treatment with iron does not correct these changes that carry into adulthood [2, 6].

Cognitive and motor functions in iron deficient non-anemic and anemic rat and mouse models have been described. The developmental abnormalities were not reversible with iron therapy indicating the importance of adequate iron during gestation and lactation to ensure appropriate brain development and myelination [10].

## Human Studies: Effects of ID

### *Infants and Children*

Several studies in infants and children have been carried out in the last few decades [5]. ID plays an important role in the motor and cognitive development of children. A significant correlation has been found between iron deficiency anemia (IDA) and cognition. The question whether the effect is due to IDA or ID without anemia has also been answered to some extent. ID without anemia has an effect on cognitive and motor scores although once IDA sets in a more severe ID is associated and the scores tend to be lower [5].

Children with all stages of ID have been tested for cognitive and motor development (IDA, ID, iron depletion along with iron sufficient groups). In addition to the degree of anemia, duration and chronicity have also been examined. Initial studies were carried out at 6 months to 23 months [5, 11, 12], children were tested before and after treatment with iron (oral/IM) short term [13], for 3 months and after 6 months [5, 11, 12].

The same cohort of children were examined again at 5 yrs (at school entry) and at 11–14 yrs and subsequently at 19 yrs for assessing long term effects of anemia on mental and motor functions before and after iron therapy in infancy [5, 11, 12, 14].

Infants are particularly vulnerable in the time period of 6–23 months. ID at this age is highly prevalent and during this period there is growth spurt of the latter part of the brain and is associated with unfolding of fundamental, mental and motor processes.

## Developmental Deficits

### *Mental, Motor and Behavioral Effects: Infants and Young Children*

In ID, reduced mental, motor, social/emotional and neurophysiological functioning have been observed. The impact of ID on social and emotional behavior of infants is wariness, hesitancy, solemnity, unhappiness and keeping closer to their mothers. Several studies indicate a negative effect of iron deficiency [5, 11–13].

Lozoff et al. [5, 11] observed both mental and motor scores were reduced in infants with Hb <10 g/dl and only motor scores were reduced in children with Hb 10.1–10.5 g/dl. Infants with lesser degrees of ID i.e. iron deficient and iron depleted children showed no impairment [5, 11]. Anemic infants in all age groups seemed to have trouble with particular motor functions involving balance and coordination. Differences in mental and motor scores remained statistically significant after correcting for factors related to birth, nutrition, family background, lead, perinatal IQ and home environment. It is interesting to note that after 3 months of therapy with iron, anemia was corrected in all, but 64% had biochemical evidence of ID. Previously anemic infants continued to have lower mental and motor development. A small number of children who became iron sufficient after 3 months of therapy with iron showed higher test scores. Severity of chronicity (anemia >3 months duration) led to lower developmental scores. Extending iron treatment for 6 months did not improve the scores.

Similar findings were obtained on a long-term study on infants in Chile. Walter et al. (1989) [12, 14] studied full term infants administered iron for 3 months, in a community clinic from Chile in a Food Fortification Study at 3, 12.5 and 15 months using Bayley scales of infant development. Mental scale assessed cognitive skills, language acquisition and abstract thinking, and motor/psychomotor scale measured gross motor abilities i.e., coordination, body balancing and walking.

On the other hand, complete reversal of mental and psychomotor, has been reported in Indonesian children after 4 months of therapy with iron [15].

Ortega et al. [16] observed better school capability in Spanish 15–16 yr school children with higher hematologic parameters and ferritin concentration. Hemoglobin correlated with calculus capability. This observation is reinforced by a large study on 5,398 children followed from infancy, 6–16 yrs from the US. Children with ID with or without anemia were more than twice at risk of having problems with mathematics [17]. Iron deficient Thai children scored significantly lower than iron-replete children [18].

In addition, some studies have observed no differences in mental or motor scores test scores in anemic and non-anemic children: infants of low-income Mexican-American population [19] and in 11–13 month children among a group of infants with low serum ferritin levels and a second group with intermediate ferritin levels or babies with higher ferritin values [20].

Seshadri and Gopaldas (1989) [21] found that 8 months of iron therapy in Indian schoolchildren improved certain scores on a battery of cognitive tests. They reported differential results on cognitive test scores: improved scores in 5–7 yr old children and 8–15 yr old anemic

and non-anemic girls, but no change in 7–8 yr old children and 8–15 yr old boys.

Lower values in WICS items of information, comprehension and verbal, performance and full scale IQ were found in 6–12 year old Mexican iron deficient non anemic children compared to controls. EEG power spectrum of iron deficient children had a slower activity than in iron replete children suggesting a developmental lag and/or a CNS dysfunction [22].

Agaoglu et al. (2007) [23] from Turkey studied 30 iron deficient children on iron therapy for 4–6 months and matched 6–12 year control children and observed significantly lower IQ ratios between iron deficient and control children ($p<0.01$). Post-treatment, the IQ scores (WISC-R intelligence test subsets) were significantly higher ($p<0.01$) in the anemic group.

In children of higher age groups (12–14 yrs) also, anemic children scored lower on achievement tests than the non-anemic controls, were also lower on visual after-image tests and displayed more behavioral problems [5, 17]. Correlations have been observed between hemoglobin and language achievement. Non-anemic Egyptian children were faster and more accurate on the matching familiar figure test [18]. Treatment with iron in anemic children tended to improve achievement scores, although they did not reach the score levels of non-anemic children indicating either incomplete correction of ID or irreversibility of the deficit or other factors.

### *Long-term Effects of IDA in Infancy and Young Children*

Children who were anemic and iron deficient as infants or toddlers were more likely to have lower test scores when retested at the time of school entry at the age of 5 yrs than control children on each test or sub-test in the cognitive battery [5, 18]. Lower hemoglobin concentration at 8 months predicted poorer locomotor development at 18 months. Correlation of IQ at 5 yrs was found with hemoglobin at infancy (at 9 months). IQ at 4 yrs could also be predicted by hemoglobin at 5 months and 36 months. Further, there is persistence of behavioral changes and lower mental scores at 5 and 7 yrs [5, 18] and requirement for anemic infants of special education classes at 10 yrs of age, as observed from data of birth and school obtained from WIC, i.e. Women, Infant, and Children, a US federal program providing nutritional assistance, which is a disturbing observation[18].

Children retested after infancy at 5 yrs and 11–14 yrs, scored lower in arithmetic and writing achievement and motor functions, continued to have problematic behavior and required 2–3 times the number of special education classes. The mental gap increased further by the age of 19 yrs in iron deficient anemic children [5].

Subsequently, some preventive studies in well-nourished infants show a positive effect on motor development [24, 25].

A review of several studies led to a differential conclusion that iron supplementation improves mental development score moderately in children >7 yrs, but not on mental development in children <27 months or motor development [26].

## Neurophysiologic Effects in ID

### *Evoked Response Potentials (ERPs) in ID*

Several tests of cognition are available, some of which have a subjective factor of learning during the period of testing. Auditory brain responses (ABRs) are a non-invasive measure of examining an aspect of CNS. ABRs represent progressive activation as the CNS matures at different levels of the auditory pathway, from the distal part of the acoustic nerve (Wave I) to the lateral leminiscus (Wave V). The auditory pathway checks the time for processing the stimulus for the acoustic nerve transmission of wave I to wave V at the lateral leminiscus. This is the Central Conduction Time (CCT) and is an index of CNS development because myelination of nerve fibers and maturation of synaptic relays reduces the CCT exponential from birth to 24 months of age [27].

Studies using ERPs (auditory [ABR] and visual evoked responses [VEP]) in iron deficient children show prolonged latencies and reduced amplitudes of waves. Prolongation of latencies is probably due to impaired myelination, although several pathways in the brain are affected. Slower transmissions as measured by ABR and VEPs have been observed in Chilean infants with IDA at 6–18 months which are uncorrected by iron therapy [28]. Repeat studies at approximately 4 yrs of age on the iron deficient anemic children continued to show prolonged latencies for all ABR waves and interpeak latencies. This finding supports the hypothesis of essential requirement of iron for myelination in early infancy. This was the first evidence that effects of IDA in infancy on pathway transmission in both the visual and auditory systems can be long lasting [29].

A study [30] from India was carried out on 36 children of which 19 were iron deficient and 17 were control non-anemic children with a mean age of 7.53±4.29 yrs. Anemic children had hemoglobin of <12 g/dl. ABR showed significantly increased latency of wave IV ($p<0.05$) as well as increased latencies of waves I, II, III and V.

Subsequent prospective cognitive and anthropometric studies were carried out measuring ERPs and cognitive functions in anemic and control school children before and after the treatment [31]. The study was carried out in male and female children aged 8–10 yrs, belonging to classes IV and V from the lower middle class socioeconomic status. Of 800

children examined, 400 were excluded, 110 formed the study group and follow-up was completed in 94. Hb was <12 g/dl in the anemic group and ≥12 g/dl in the non-anemic control group. Anemic children were treated with 3–4 mg/kg/day of elemental iron per day for 12 wks. Both anemic and control groups were also given vitamin C 100 mg/day and albendazole to eradicate intestinal worms. Iron parameters and neurophysiologic measurements were made pre- and post-treatment. Tests for cognition included: P300 latency, P300 amplitude, Ravens test gross score, Ravens test percentile rank, Derived intelligence quotient, Digit span attention test gross score, Digit span attention test: Thet quotient (TQ). There was a decrease in cognitive functions in anemic children, some of which were significantly lower. P300 latency was increased in both girls (unpublished data) and boys [31] and was significantly lower compared to control children. Post-treatment hemoglobin levels increased in both girls and boys, the increase was greater in the girls. Cognitive functions improved and P300 latency decreased in both girls and boys. The decrease in P300 latency was statistically significant in the girls ($p<0.05$). Although there was a reduction in latencies, longer therapy with iron may be required for further correction of cognitive functions and P300 latency in the children. This may indicate whether complete correction can be obtained or beyond a certain level the defects are irreversible. It is interesting to note that children in the control group showed an increase in hemoglobin and improvement in cognitive functions which was probably due to the increase in iron absorption (effect of vitamin C) and reduction in worm load, if any (albendazole). It was also not possible to exclude the absence of ID in control children, as serum ferritin was not measured. Bandhu et al. (2003) [32] also observed that IDA children lagged behind the control children in terms of anthropometric parameters and they benefited relatively more in terms of anthropometric and hematological improvement after iron supplementation.

Li et al. (1994) [33] found direct correlation between severity of ID and abnormalities in ABR in 48 ID infants. Sarici et al. (2001) [34] observed prolonged N2 latencies in visual evoked potentials in 20 iron deficient infants and its reversal after treatment with iron. However, no significant differences were observed in ABRs between iron deficient and control children [35].

Nawal et al. (2009) [36] showed a significantly lower IQ score and prolongation of ABR latencies in 30 iron deficient children aged 2–5 yrs compared to matched controls, and significant linear correlation with hemoglobin levels. ABR latencies and interpeak latencies were significantly prolonged and amplitudes significantly lower in children with IDA. EEG showed that the anemic group had focal changes with a higher risk for epilepsy.

A study carried out on 33 Turkish infants and children with IDA and 31 healthy controls were compared in three age groups: 0–12 months, 13–36 months and 37–60 months. Significant differences in different waves of ABR were found in all three ID groups compared to controlled groups ($p<0.05$, $p<0.005$ and $p<0.05$, respectively) [37].

Auditory and visual recognition ERPs in 15 iron deficient infants were compared to 19 iron sufficient infant [38]. The iron sufficient group showed greater response to mother's face and a greater updating of memory for the stranger's face at 9 months of age. In the deficient group, it was not seen till 12 months suggesting a cognitive developmental delay associated with ID.

Recent studies in newborn infants of diabetic mothers observed similar effect of ID on the auditory recognition memory in the newborns. ERPs in response to speech vs non-speech sounds and the response to mother's voice vs stranger's voice were measured. Peak latencies were reduced in the iron deficient newborns. In addition, a significant negative slow wave was observed in response to mother's voice vs the voice of a stranger in iron sufficient newborns and not in iron deficient newborns. This is probably due to the effect of ID on the development of the hippocampus [39].

Iron supplementation in infants with birth weight less than 1,301 g, on follow up showed that early oral iron demonstrated a trend towards a beneficial effect on long term neurocognitive and psychomotor development evaluated at a median age of 5.3 years [40].

Perinatal effects of maternal ID have been observed on neonates (temperament like behavior) [41]; supplementation has been beneficial for motor development and visual acuity at 12 months [5, 25].Recent evidence suggests the metabolism of a number of drugs whose target of action is reuptake of monoamines may be dramatically altered by existing brain iron deficiency [42]. This, in turn, may affect drug efficacy,

The effect of ID on childhood growth is often difficult to separate from overall nutritional deficiency. However, when the two factors have been separated, correction of ID improves growth independent of nutritional status.

ID affects the brain i.e. the central nervous system in infants, children, adolescents and even adults. The question arises of reversibility by treatment with iron. Correction of the deficiency in the population should be considered urgently as ID is rampant in India and a large cohort of children will grow up and eventually have psychomotor and neurological defects. Treatment with iron is cheap and reverses some of the effects as has been observed in a large number of studies although compliance may be a problem. However, in view of the serious behavioral changes observed in ID in infancy, which persist in spite of iron therapy given later, it is imperative to prevent ID in infants and pregnant and lactating women.

These studies clearly demonstrate that ID causes a diminution in developmental and neurophysiologic cognitive

functions and treatment with iron can reverse the effects to some extent. However, long-term studies are required to assess the effect of iron therapy on cognitive functions in Indian children. This becomes important as a very large population is moderate to severely iron deficient and defects in cognition in the children have far greater implications.

Increasing awareness in the medical fraternity and the population in general, of the deleterious effects of ID, some of which are subtle and subclinical and likely to have a long-term effect, may be one step towards this goal.

This is particularly relevant in view of the widespread prevalence of anemia in India as seen from the recent reports of National Family Health Survey-3 (NFHS-3), which shows an increasing trend of anemia in all population groups compared to the previous survey [43].

The prevalence of anemia as per NFHS-3 (2005–06) shows a higher prevalence of anemia in all groups of population tested compared to NFHS-2 (1998–99) [44]. The prevalence of anemia as per NFHS-3 was 79.2% in children 6–35 months, 56.2% in ever married women 15–49 yrs, 57.9% in pregnant women 15–49 years and 24.3% in ever married men.

## Other Neurological Sequelae of ID

In addition to developmental delay, pediatric stroke, breath holding spells, pseudotumor cerebri, and cranial nerve palsy have been described. ID responsive to treatment with iron has been associated in these conditions [45].

Recently Konofal et al. (2005) [46] reported a 3-yr old male child with ADHD (attention deficit/hyperactivity syndrome) and low serum ferritin who responded to iron therapy given for 4 months, with increase in serum ferritin and decrease in the Connor's Parent and Teacher Rating Scale.

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