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Iron deficiency and neural development: An update

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SUMMARY. In Latin America, 10-30% of reproductive age females and upwards of 40-70% of pregnant women may be iron deficient. The true prevalence in young children and infants is often hard to determine because of problems in survey design, data collection, or sampling. There is little doubt, however, that iron deficiency anemia is a significant nutritional problem in many infants within the first 5 years of life. 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 the alteration in cognition that occurs in iron deficient individuals during the early parts of their life cycle and perhaps at later times as well. While iron deficiency was once presumed to exert most of its deleterious effects only if anemia was present, it is now clear that many organs show morphologic, physiologic, and biochemical changes before there is any drop in hemoglobin concentration. Iron deficiency is associated with alterations in many metabolic processes that may impact brain functioning; among them are mitochondria electron transport, neurotransmitter synthesis and degradation, protein synthesis, organogenesis, and others. It is necessary to separate the developmental aspects of iron deficiency and neural functioning from the aspects of iron deficiency that could occur at any time in life. A number of reviews have discussed the links between brain iron and neuropathology, brain iron, nutrition, and development, and iron status and cognition. New knowledge concerning the acquisition of iron by the brain in early life is being generated by numerous research groups. In the next decade a much clearer understanding of the role of brain iron on neural functioning will probably emerge.
Keywords: Iron deficiency, cognition, brain iron, neural functioning.

RESUMEN. Deficiencia de hierro y desarrollo neural: Una visión actual. En América Latina del 10-30% de las mujeres en edad reproductiva y por encima del 40-70% de las mujeres embarazadas pueden tener deficiencia de hierro. La verdadera prevalencia en lactantes y niños es difícil de determinar por problemas de diseño de encuestas, recolección de datos y muestreo. Sin embargo, existe poca duda de que la anemia por deficiencia de hierro es un problema significativo en muchos niños menores de 5 años. Numerosas intervenciones se han realizado con variados grados de éxito y es claro que casi todas las intervenciones la deficiencia de hierro es prevenible al igual que sus consecuencias. Una de estas consecuencias es la alteración en el desarrollo cognoscitivo que ocurre en individuos deficientes en hierro durante los primeros períodos de su vida y quizás posteriormente también. Aunque se creía que la deficiencia de hierro era más dañina sólo en presencia de anemia, es claro ahora que muchos órganos muestran cambios morfológicos, fisiológicos y bioquímicos antes de la disminución en los niveles de hemoglobina. La deficiencia de hierro está asociada a alteraciones en muchos procesos metabólicos que afectan el funcionamiento cerebral, como el transporte de electrones en la mitocondria, la síntesis y degradación de neurotransmisores, síntesis de proteínas, organogénesis y otros. Es necesario separar los aspectos de desarrollo de la deficiencia de hierro y el funcionamiento neural de los aspectos relacionados con la deficiencia de hierro que ocurren en cualquier momento de la vida. Varias revisiones han discutido la relación entre el hierro cerebral y las neuropatologías, hierro cerebral, nutrición y desarrollo y hierro y aspectos cognoscitivos. Continúan surgiendo nuevos conocimientos acerca de la adquisición de hierro por el cerebro en edades tempranas y se espera que en la próxima década se tenga un mejor entendimiento acerca del hierro cerebral y el funcionamiento neural.
Palabras clave: Deficiencia de hierro, cognitivo, funcionamiento neural, hierro cerebral.

Iron deficiency is the most common single nutrient deficiency in the world. It affects the lives of more than 2.1 billion people, with estimates of more than 50% of women of reproductive age and similar percentages of adolescents being iron deficient (1). In Latin America, 10-30% of reproductive age females and upwards of 40-70% of pregnant women may be iron deficient. The true prevalence in young children and infants is often hard to determine because of problems in survey design, data collection, or sampling. 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 the alteration in cognition that occurs in iron deficient individuals during the early parts of their life cycle and perhaps at later times as well (2). There is a history of nearly 30 years of efforts to document the effects of iron deficiency anemia on developmental delays in young children and infants (3-6).

Iron needs of the brain vary with the stage of the life cycle and the cell types that inhabit the Central Nervous System.

Iron is the key component of the many enzymes that involve essential oxidation-reduction reactions, synthesis of neurotransmitters, catabolism of neurotransmitters, and synthetic processes such as the production of myelin (60). While it is common to think about iron metabolism in the brain from a nutritional perspective, it is important to recall that iron is toxic to cells in the free state and several neuropathologies appear to have an iron accumulation component. One recent example of this is the disease, Friedrichís ataxia. In this disease there is an excess accumulation of iron in the mitochondria with a resulting neuronal death. It is believed that the fundamental defect is the failure of a frataxin gene product to be appropriately expressed resulting in poor transport of iron out of the mitochondria (64).

Acquisition of iron: The brain likely obtains iron via transferrin receptors expressed in endothelial cells on the brain microvasculature (7, 8). The movement of iron across this blood-brain barrier is likely affected by the iron status of the endothelial cells that comprise the barrier, as well as the astrocytes on the basolateral surface of the microvascular bed (55). The regulation of iron movement across this barrier is not well understood. The rate of iron uptake into the brain is affected by the iron status of the animal, increasing when the iron status is low and vice versa (9). In addition, the process is highly selective and not reflective of overall blood brain permeability (10,11). The uptake of iron is reported to be homogeneous followed by a redistribution of iron to the basal ganglia (12). Regions of the brain rich in iron in adulthood (i.e.: substantia nigra) are far less affected by iron deficiency than are other regions like the cortex or the striatum (13). Autoradiographic studies reveal a heterogeneous distribution of transferrin receptors in the adult brain (14,15), though studies of the relationship of this distribution to systemic iron status have not been published. The regional heterogeneity in the deposition of iron in the brain is remarkably similar across many species with the basal ganglia, substantia nigra, and deep cerebeliar nuclei particularly rich in iron (16). When magnetic resonance imaging was used to map iron distribution in the brains of children and adolescents, the highest concentrations of iron were found in globus pallidus, caudate nucleus, putamen, and substantia nigra (17). Recent studies from our laboratory and those of associates now demonstrate that the rate of iron accumulation in different brain regions is a function of the stage of brain development that is occurring at the time of the investigation (58). For instance, when brain iron distribution is studied in a rodent model of lactational iron deficiency; an entirely different pattern of iron loss emerges compared to the effects of iron deficiency instituted during the post-weaning period. Thus the needs for iron in the brain are very developmentally bound in early life with clear ramifications in functioning of some brain regions while having little impact in others. Recent studies in our laboratory demonstrated that pre and post-weanling iron deficiency result in very different patterns of iron loss in different brain regions (60,58). In the lactational iron deficiency period (equivalent to humans between 6-12 months of life); there is a very significant 25% drop in cortex, striatum, and hind-brain iron content. In contrast, there is only a 5% drop in thalamus iron content. During post-weanling iron deficiency there are comparable 20-30% declines in cortex, striatum, and hind-brain, but now, the thalamus also becomes sensitive to dietary iron deficiency and demonstrates a 20% drop in iron concentration. These studies demonstrate that the impact of iron deficiency on brain iron content is dependent on the timing of the nutritional insult compared to the brain growth occurring at that time.

Iron and transferrin levels have to been reported to be high in cerebrospinal fluid (CSF), especially in perinatal brains (18). The actual levels of iron in CSF however are poorly described in conditions of iron overload, iron deficiency, or during active growth and development. Our experience using atomic absorption spectrophotometry reveals CSF iron concentrations of approximately 15-25 ug/L in humans and monkeys, and 5-20 ug/L in mice (59,62). These concentrations are about 5-10 fold lower than the corresponding plasma concentrations. The choroid plexus is a rich source of transferrin mRNA, and transferrin is secreted by this organ presumably for use in the distribution of iron to glia and neurons for use or storage (19). The normal circulating level of Tf in CSF is also poorly described, though some reviews of the literature suggest the total iron binding capacity (TIBC) of the CSF is barely even with the circulating CSF iron concentrations resulting in the apparent availability of "free iron" (62). Our own experience with measurements of Tf and TIBC in CSF of humans, monkeys, and rodents however do not support this contention (unpublished data). The role of the CSF in the delivery of iron to various brain cells is not well understood. Iron appears first in the choroid plexus in some studies, and then re-distributes to other regions of the brain (63,61). Movement of iron from the choroid plexus to other parts of the brain imply a role for Tf, and perhaps other iron containing proteins, in this re-distribution (57). The exact identity, and mechanism of regulation in response to changing iron needs is being actively investigated by several laboratories at this time.

The predominant cell type containing iron in the mouse, rat, monkey, pig, and human brain is the oligodendrocyte (20). These cells are responsible for the production of myelin and hence alterations in the functioning of these cells are associated with hypomyelination. When oligodendrocyte maturation is disrupted, as occurs in myelin genetic mutants, iron accumulation is only about 50% of normal (21). In iron deficiency oligodendrocytes appear more "immature" (13).

Brain transferrin is made by oligodendrocytes and choroid plexus, although early in life it is likely derived from the plasma pool, since the blood-brain-barrier is not complete and the transferrin mRNA expression in these cells is low at that time (4). While there is no quantitative data to show that iron

deficiency leads to a lesser number of oligodendrocytes, hypomyelination occurs as a result of post-natal iron deficiency. Transferrin levels in the brain and cerebrospinal fluid fall from birth through 2 years of age, and can be affected by alterations in oligodendrocyte function (22). Rats exposed to a low iron diet after weaning have a doubling of brain transferrin content within 14 days of dietary iron restriction, reflecting a need for increased iron delivery and associated with lowered brain iron levels (13,23).

Ferritin consists of 24 protein subunits made up of different ratios of two isoforms; the L chain (19kD) and the H chain (21kD), to form a 450kD protein capable of binding in excess of 4000 atoms of iron. The brain ferritin is richer in the H isoform than in the L, and its localization is cell type specific (8,24). In rats, microglia and oligodendrocytes contain ferritin, whereas in mice astrocytes are ferritin positive. Ferritin levels correlate with brain iron content, and are highest at birth and decline thereafter in the newborn rat (25). Moreover, the concentration can be directly affected by the body iron burden (23). Ferritin isoforms are heterogeneously distributed in brain and seemingly, not all regions of the brain are equally sensitive to an alteration in body iron status (13,26). A recent study in young rats demonstrated that there is a shift in ferritin containing cell types in early post-natal life. During the first several days of post natal life the predominate cell containing ferritin are microglia and then soon after weaning, the predominate brain cells containing ferritin become the oligodendrocytes. H-ferritin, but not L-ferritin, was present in neuronal nuclei in the cortex (54). These data suggest that microglia play a role in iron homeostasis during early brain development and perhaps complete with oligodendrocytes and thus modulate the myelination processing of the oligodendrocytes. Studies in post natal iron deficiency involving H:L ferritin ratios in pig brain reveal a dramatic effect of iron deficiency an the expression of these two subunits of the ferritin molecule (56). The developmental roles of the two subunits, relative to iron storage or utilization and detoxification are unknown, although accumulation of iron in certain brain regions is believed to play a role in a number of neuropathologies (53).

Iron deficiency and neural functioning in humans: While iron deficiency was once presumed to exert most of its deleterious effects only if anemia was present, it is now clear that many organs show morphologic, physiologic, and biochemical changes before there is any drop in hemoglobin concentration (3,4,28). Iron deficiency is associated with alterations in many metabolic processes that may impact brain functioning; among them are mitochondria electron transport, neurotransmitter synthesis and degradation, protein synthesis, organogenesis, and others. Thus, it is not reasonable to assume that only very young infants or children are susceptible to the ill effects of iron deficiency. Indeed, in a report published in Lancet in 1996 non-anemic iron deficient adolescents had significant alterations in both memory (spatial) and attentional functions that was repaired with iron therapy (29). The animal studies of brain iron content during development demonstrate that iron deficiency in early life (prior to weaning) likely has long term effects that may be only partially reversible (30). In contrast, iron deficiency that occurs later in life (the post-weaning model) also had severe effects but they were readily reversible and of a different nature (13,31,32). Thus, the timing of iron deficiency seems critical to the severity and reversibility of its impact.

Observations of altered mental and motor development have been repeatedly made in young iron deficient children (5,33,34,50,51). Both the severity and the duration of the deficiency have been noted as significant factors (35). The earliest studies of Oski and colleagues (36) observed significantly lower Bayley developmental scores in iron deficient than control infants. The scores of iron deficient children were corrected within a short period of iron treatment. This theme of alterations in mental development and behavior as a function of early life iron deficiency was expanded upon by Lozoff and colleagues in several studies (5,37,38) as well as by Walter and colleagues (6,39). With moderate anemia, many of the children were considered to have abnormal affective behavior; in severe anemia (< 9 g/dL), all of the children were classified as abnormal. Lozoff further notes a decrease in close contact between anemic children and their mothers. This may be a manifestation of their affect, energy level, and voluntary activity (33). Since cognitive and behavioral development are strongly affected by the amount and level of environmental stimulation, this indirect route of impact should not be ignored.

Importantly, the studies of Lozoff as well as those of Walter (5, 6, 37-39) note a failure to improve performance in many of the anemic children after iron therapy despite hematologic normalization. In 1993, the research team headed by Pollitt demonstrated a normalization of developmental scores in infants who were anemic by providing a vigorous iron intervention for 4 months (40). While the reversibility of cognitive as opposed to developmental aspects of behavior have yet to be demonstrated, this study provided encouraging evidence for the benefit of improving iron nutritional status in infants.

Lozoff and colleagues have been interested in the possibility that iron deficient anemic infants are "functionally isolated" (52). The behavior of 52 Costa Rican 12-23 -month-old infants with iron deficiency anemia was contrasted with that of 139 control infants with better iron status. The investigators observed the infants during free play and also tested the infants with standardized motor and mental protocols. Infants with iron deficiency were more wary, hesitant, and easily tired; made fewer attempts at test items, were less attentive to instructions, and were less playful. In addition, the adults around the iron deficient infants interacted with them less. These data support the hypothesis that iron deficient anemic

infants engage less with their environment and in return, receive less stimulation from their environment. While this model also argues for the possibility of a generalized "nutritional stress" associated with decreased affect and activity, it does not exclude the possibility that direct biologic effects of iron deficiency may result in these outcomes. The task of assigning clear roles for iron deficiency anemia in developmental delays or specific cognitive tasks is difficult (49).

Neurobiological sequelae of iron deficiency: When animals are given low iron diets in post-weaning life, there is a significant decline in brain iron content and a rapid repletion with refeeding (13,23). This is in contrast to neonatal or pre-weaning iron deficiency in which the effects appear irreversible (30,41,42). Based on animal studies across a number of species we assume that human brain iron content goes down with a decrease in body iron status, although there is no direct proof of this.

Iron is required for proper myelination of the spinal cord and white matter of cerebellar folds (43) and it is a co-factor for a number of enzymes involved in neurotransmitter synthesis including tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine and dopamine). Iron is also a co-factor for ribonucleotide reductase, the rate limiting step in DNA synthesis. Thus, it is easy to postulate that deprivation of iron to the brain during periods of very active myelination could result in poorly functioning neurons. Dr. Walter reported at the International Nutrition Society meetings in August of 1997 that iron deficient infants have a decreased nerve conduction velocity when auditory evoked potential studies are conducted, an observation consistent with improper myelination.

To date, the dopaminergic system in the only neurotransmitter system in the CNS that has been consistently responsive to experimental changes in iron status. As whole brain iron content drops 15% below normal, biologic and behavioral alterations occur as a result of changes in the dopaminergic system (44,45). These scientists measured affinities and densities for dopamine D1 and D2 receptors, serotonin, γ-aminobutyric acid, benzodiazepine, α and ß adrenergic, and muscarinic-cholinergic receptors in brain regions after post-weaning dietary iron deficiency. Iron is colocalized with dopaminergic neurons (20,46) and cell bodies throughout the brain with a lesser colocalization with γ-amino butyric acid. There are four major dopaminergic tracts in the brain. Two of these tracts pass from the substantia nigra to and through the caudate nucleus and putamen (also called the striatum). It is precisely in these areas that iron is in highest concentration, and that neurobiologic changes occur when dietary iron deficiency is created. Recent in vivo animal data demonstrate that extracellular dopamine is elevated in iron deficiency and it returns to normal levels when brain iron content and iron status return to normal (47). Attentional processing of environmental information is highly dependent on appropriate rates of dopamine clearance from the interstitial space, which suggests that iron status may be affecting behavior through effects on dopamine metabolism. Alterations in dopamine in the mesolimbic and the nigrostriatal tracts are associated with changes in motor control as well as altered perception, memory, and motivation. The loss of affect, arousal, and perception are often the characteristics that investigators associate with iron deficient infants, children, and adolescents (40).

Irreversible alterations in brain iron content have been shown in animal studies by feeding rats low iron diets early in life, prior to the completion of the brain organization, myelination, and the establishment of the dopaminergic tracts (42, 48). A significant caveat to the observations from these rodent studies is that much of the rodent brain maturation occurs post-natal. However, in species like humans whose brain growth is slower and spans significant pre-natal and post-natal periods, the sensitivity of various brain processes to the nutritional insult may be different.

In summary: A number of reviews have discussed the links between brain iron and neuropathology (27), brain iron, nutrition, and development (2-4), and iron status and cognition (39). We are still ignorant about many of the biologic details concerning the relationship of body iron status, development, and brain functioning, and most importantly we are severely lacking neurobiologic explanations for the consistent changes in attentional processes in young people. Dopamine biology may be significant, but other neurotransmitter and neuropeptide systems not yet thoroughly examined may also play very significant roles. New knowledge concerning the acquisition of iron by the brain in early life is being generated by numerous research groups. We are hopeful that in the next decade a much clearer understanding of the role of brain iron on neural functioning will emerge.

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