Introduction

Iron deficiency is the most common nutritional disorder in the world, both in developing and industrialized countries. This deficiency is the leading cause of anemia, and is most prevalent in women and children (1). In addition, it has long been suspected that iron deficiency correlates with poorer cognitive and behavioral performance (2). However, despite progress made in describing the biochemical effects of iron deficiency, it has been difficult to isolate the cognitive and behavioral effects of iron deficiency alone. Complicating this is the large number of confounding factors associated with iron deficiency, such as socioeconomic and other nutritional factors (3).

Why study the effects of iron deficiency in non-anemic children? Simply put, non-anemic children with iron deficiency are less likely to be treated. In the United States, infants at high risk for iron deficiency are usually screened for anemia with hematocrit measurements by age 12 months. However, many iron deficient infants are not detected with this screening procedure (4). For every child that is deemed iron deficient through hematocrit testing, several more are not detected at all. By better understanding the effects of iron deficiency without anemia, the need for more thorough iron testing in children can be evaluated.

Who is Affected?

In the United States, it is estimated that 9% of toddlers (age 1 to 2 years) are iron deficient, corresponding to about 700,000 toddlers nationwide. Iron deficiency anemia is estimated to exist in 3% of (or 240,000) toddlers (5). Consequently, for each toddler detected as iron deficient through anemia, nearly two iron-deficient, non-anemic toddlers go undetected.

A similar problem exists in young females. While it is estimated that 9% to 11% of all adolescent girls and women of childbearing age are iron depleted (about 7.8 million nationwide), only 2% to 5% (about 3.3 million) have iron deficiency anemia,(5) leaving 4.5 million women undetected through conventional hematocrit screening methods. Some studies suggest the problem is even worse, with rates of iron deficiency in the US reaching nearly 25% in all adolescent girls (6).

Age-related differences aside, iron deficiency is likely to affect certain communities more than others. For instance, infants of low-income families have three times the risk of iron deficiency (4). There is also a positive association between iron deficiency in children and communities high in Southeast Asian and Hispanic populations (7). Worldwide, the problem is worse. Approximately 20% to 25% of all infants have iron deficiency anemia, with countless more iron deficient without anemia (8).

Thus, millions of children in the US, and millions more worldwide, suffer from inadequate iron intake during a time of substantial neural and cognitive development. This fact underlies the importance of understanding the effects of iron deficiency on cognitive and behavioral function.

Biochemical Effects of Iron Deficiency

A variety of research over the past several years has demonstrated that iron deficiency can cause morphologic, physiologic, and biochemical changes in many organs before a drop in hematocrit occurs (9). This strengthens the argument that the effects of iron deficiency are independent of the symptoms of anemia. Of particular importance are those biochemical changes that may affect neural metabolism and functioning.

Plasma transferrin can cross the blood-brain barrier, and is at a higher concentration in the CSF than in the blood plasma (10). It has been shown that iron is required for several neurological metabolic processes, including neurotransmitter synthesis, myelin formation, and brain growth (11,12). It has also been demonstrated that iron distribution in adult brains is heterogeneous and different from iron distribution in developing brains (12,13). This evidence suggests that iron plays a significant role in the developing central nervous system. Consequently, iron depletion during neurological development could significantly impact a wide variety of cognitive and behavioral functions.

What brain functions are most likely affected? The highest iron concentrations in the adult brain are found in the basal ganglia, substantia nigra, and deep cerebellar nuclei, which are known to be involved in motor control and coordination (8,13). Iron deficient individuals show a selective decrease in dopamine neurotransmittion, which is also involved in motor control (14). Dopamine transmission is also involved in the prefrontal-striatal system, which is involved in spatial/working memory and selective attention (8). Additionally, dopamine plays a significant role in attentional processing of environmental information (10).

This evidence suggests that iron deficiency can potentially affect multiple cognitive functions, including motor control, memory, and attention. Because of iron's role in the development of these neural systems, it may be postulated that iron deficiency in children would alter the development of these processes, perhaps permanently. Such neurological changes would likely be expressed behaviorally in certain motor tasks, scholastic achievement, and/or problem-solving skills.

Cognitive and Behavioral Effects of Iron Deficiency

As described in the previous section, there is enough biochemical and neurological evidence to suggest how iron deficiency might express its symptoms in children. Are these symptoms seen in iron deficient children?

Results in Iron Deficient, Anemic Children

An exhaustive review of dozens of studies concerning the effects of iron deficiency anemia on cognitive development was recently published in The Journal of Nutrition (February 2001) (3). The authors concluded that most of these studies show consistent evidence for poorer cognitive and motor development, poorer scholastic achievement, and increased behavioral and disciplinary problems in iron deficient children. Although the effects of anemia may compound these results, they are at least consistent with the idea that iron depletion causes cognitive and motor deficiencies.

Results in Iron Deficient, Non-Anemic Children

Iron deficiency in non-anemic children has not been studied as extensively as iron deficiency anemia. Most research focuses either on anemic children or iron deficient children without regard to anemia. Despite the fewer number of studies done on non-anemic children, the results are generally consistent with those of iron deficient anemic children, although the results are more dramatic when anemia is present.

A review by Pollitt et al (2). of several studies on iron deficient children with and without anemia between 1976 and 1986 gave results mostly consistent with biochemical evidence mentioned above.

That is, both anemic and non-anemic iron deficient children showed lower scores of mental development and poorer problem solving skills. However, there was no evidence for delayed motor development in either group compared to iron replete children.

More recently, a study (15) in Mexico compared iron deficient non-anemic children (6 to 12 years old) to normal children and found significant differences in cognitive performance and brain waves between the two groups. Specifically, iron deficient children showed significantly lower scores on tests of verbal, comprehension, and performance IQ, as well as overall IQ. Furthermore, electroencephalogram results indicate that iron deficient children show slower brain wave activity. These results are suggestive of either a developmental lag and/or a central nervous system dysfunction.

Another study,(16) in Thailand, found results consistent with both experiments mentioned above. They found an association between iron levels and IQ in 11-year old school children, although the authors admit there is no evidence for a causal relationship.

Finally, a US study (6) conducted on non-anemic, iron deficient high school girls found that iron supplements given over 8 weeks can significantly improve cognitive functions. This was a double-blind, placebo-controlled study. Implications of this are considerable, since it suggests that some effects of iron deficiency can be reversed. However, more research of this type needs to be conducted, since there was no control for iron supplements given to iron replete subjects. Also, this study does not address the age at which these girls became iron deficient, nor how long they have been so.

Animal Studies
Multiple animal studies have supported the idea that early iron deficiency causes cognitive impairment of certain tasks (3). For instance, it has been shown that mice born from mothers who were fed a low iron diet showed poorer performance in cognitive tasks compared to normal mice. This experiment also demonstrated that postnatal iron supplementation had no effect on these cognitive deficiencies. These results suggest that iron plays a critical role in neural development, and that these effects are permanent (17). The implications of this study are enormous, since pregnant women are more likely to be iron deficient that others due to fetal demands. For example, 40% to 70% of pregnant women in Latin America are estimated to be iron deficient (9).

Are These Effects Permanent?
As with the animal study mentioned above, several human studies have suggested that iron deficiency at a young age can cause permanent effects. In a 10-year follow-up study in Costa Rica (8), infants who were initially iron deficient (and anemic) were given consistent iron supplements over 10 years. The results to several cognitive and motor tasks were measured before and after the treatment and compared to a control group. No improvement was seen in children who were initially iron deficient, despite the fact that they had remained iron replete and non-anemic for 10 years. Moreover, these children showed more disciplinary problems and were more likely to repeat a grade.

Contrarily, iron supplements given over 8 weeks have been shown to increase the cognitive performance in iron deficient, non-anemic high school girls (6). A study in Guatemala also showed that iron supplements given to iron deficient infants (with and without anemia) for 7 to 10 days showed an immediate improvement in mental development (2).

To this authors knowledge, there are no research papers concerning the permanent effects of iron deficiency without anemia in peri-natal infants. Although it has been shown in animals and anemic children that these effects can be permanent, it is not known if iron deficiency without anemia is severe enough to cause permanent effects.

The Problem of Confounding Factors
Unfortunately, many significant confounding factors are associated with both iron deficiency and cognitive development. These include low socioeconomic status, poverty, lack of maternal warmth and other home stimulation, poor maternal education and IQ, maternal depression, more absent fathers, low birth weight, parasitic infections, elevated blood lead levels, and overall poor nutrition (3). It is difficult for many studies to accurately control for all of these factors. Consistent results seen in animal studies support the causal relationship between iron deficiency and decreased cognitive function. However, it is very important to keep in mind the limitations of human studies.

Putting It All Together

On a biochemical level, evidence for impaired cognitive function with iron deficiency is growing tremendously. Animal models have consistently demonstrated the importance of iron in proper neural and behavioral development (3). This research has created a biochemical model that supports the necessity of adequate iron for proper CNS development. In human studies, however, things are more complicated. Despite the accumulating evidence supporting the causal relationship between iron deficiency and impaired cognitive development, complex confounding variables obscure the meaning of these results.

Additionally, most research on iron deficiency in children focuses on the effects of iron deficiency anemia. This makes it difficult to distinguish the effects of iron deficiency separate from the effects of anemia. To illustrate this point, consider the effects of anemia due to renal dysfunction. It has been well documented for over a century that patients with renal failure display altered mental states and impaired cognitive function. These symptoms include, among other things, a diminished intellectual capacity and a slowing of EEG waves. Further, these changes correlate with blood hematocrit levels, and are directly related to brain oxygen supply (18). Thus, significant cognitive changes can occur in anemia without any iron deficiency. It is, therefore, quite likely that some symptoms of iron deficiency anemia are due strictly to the anemia, not the low iron status.

Altogether, there is good evidence to support the hypothesis that iron deficiency without anemia can cause impaired cognitive function. Although the number of studies into non-anemic subjects is limited and plagued with confounding variables, these results are supported both by animal studies and evidence from iron deficiency anemia research. It seems likely that iron deficiency without anemia can impair intellectual abilities and school performance. Conflicting evidence surrounds whether these effects are permanent or treatable. Evidence does not strongly support impaired motor functions in these children. However, these conclusions must be taken with some skepticism. Not enough research has accumulated to draw firm conclusions.

Several major questions remain. What degree of iron deficiency is sufficient to impair cognitive abilities? At what developmental stage does iron deficiency cause its major effects? Do iron supplements in iron deficient, non-anemic children have long term benefits? Once these questions are more clearly answered, we will begin to understand the true importance of adequate iron status in our developing central nervous system.

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