Iron Deficiency in Infants and Toddlers in the United States

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Iron deficiency anemia (IDA) continues to be overwhelmingly the leading cause of anemia in early childhood and a global public health challenge. Although there has been a significant decrease in the frequency of IDA and iron deficiency (ID) in infants and toddlers in recent years in the United States, ID and IDA persist and the adverse effects of ID are long-lasting if not permanent. Moreover, ID can result in lead toxicity, and this toxic exposure, even with low levels, can impair neurocognitive function as well. This review describes the major steps that have taken place to decrease the frequency of ID and IDA.

Keywords infants and toddlers, iron deficiency, iron deficiency anemia

INTRODUCTION

Iron deficiency (ID) during early childhood became a public health issue in the United States during the late 1960’s. At that time prevalence rates of breast feeding were low and low-iron formulas were often used. Iron-fortified formulas were first introduced in 1959. The prevalence rates of IDA and ID were found to be very high at that time but the prevailing clinical wisdom within the pediatric community was that ID was not a serious medical problem. The most significant consequence of ID was considered to be the anemia itself. However, unless very severe, the anemia did not constitute a grave danger. It was simply an indicator of the severity of the ID. When the diagnosis of IDA was extreme, the child was simply treated with supplemental iron to correct the anemia. There was no clinical evidence that IDA in a young child could adversely affect other organ systems, including the brain.

ID AND NEUROCOGNITIVE DEFICITS

In 1983, Oski et al. [1] published the results of a study demonstrating a relationship between ID in the absence of anemia and impaired mental and psychomotor development in infants 9 to 12 months of age. Iron status was based on measurements of serum ferritin, erythrocyte protoporphyrin, and erythrocyte mean corpuscular volume, and infants were classified as iron sufficient, depleted, or deficient. Infants were tested with...
TABLE 1 Association Between Iron Deficiency and Neurocognitive Development

<table>
<thead>
<tr>
<th>Reference</th>
<th>Neurocognitive tests</th>
<th>Outcome after iron therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bayley mental development index</td>
<td>ID infants—improved score</td>
</tr>
<tr>
<td>2</td>
<td>Bayley scales of infant development</td>
<td>ID and IDA infants—improved score</td>
</tr>
<tr>
<td>3</td>
<td>Bayley scales of infant development</td>
<td>Anemia and ID corrected—improved scores</td>
</tr>
<tr>
<td>4</td>
<td>Wechsler preschool and primary scale of intelligence</td>
<td>IDA infants had lower scores at 5 years</td>
</tr>
<tr>
<td>5</td>
<td>Bayley scales of infant development</td>
<td>IDA infants had lower scores</td>
</tr>
<tr>
<td>6</td>
<td>New/old word recognition memory task</td>
<td>IDA children—decreased ability for word recognition</td>
</tr>
<tr>
<td>7</td>
<td>Denver developmental screening test</td>
<td>Achievement of developmental milestones in treated infants</td>
</tr>
<tr>
<td>8</td>
<td>Bayley scales of mental and motor development</td>
<td>Improved Bayley scores in treated infants with IDA</td>
</tr>
</tbody>
</table>

ID–iron deficiency and IDA–iron deficiency anemia

the Bayley Mental Development Index prior to and 7 days after parenteral iron therapy. Iron administration produced a significant increase in Index score in iron deficient infants (+21.6 points) but not in iron sufficient or depleted infants. This report sparked the imaginations of other investigators to study the effects of ID on neurocognitive development (Table 1) [2–8]. Notably, Lozoff et al. [4] and Congdon et al. [6] detected neurocognitive deficits at 5 and 10 years after therapy for IDA, respectively. Each group studied Hispanic children from lessersocioeconomically advantaged homes, and results were controlled for a comprehensive set of background factors.

COW MILK AND IRON DEFICIENCY

It was customary to switch a baby from infant formula to cow milk at six months of age. Breast feeding mothers who stopped at six months also switched to cow milk. Dr. Oski and others believed that this early introduction of cow milk, containing minute quantity of poorly bioavailable iron, was an important contributing factor to the high prevalence of ID and a paradigm shift for withholding cow milk until one year of age was entertained.

In 1987, Tunnessen and Oski [9] studied 69 infants fed cow milk commencing at 6 months of age and 98 infants continued on an iron-fortified formula. At 12 months of age, those fed cow milk had lower mean serum ferritin levels and mean corpuscular volume, higher free erythrocyte protoporphyrin values and greater incidence of hemoglobin values less than 11 grams per deciliter than did iron-fortified formula fed infants. They concluded that to avoid ID infants should continue to receive an iron-fortified formula throughout the first year of life or receive an iron supplement if cow milk in instituted prior to their first birthday. Indeed, Woodruff [10] and Wilson [11] point out that cow milk if started before 12 months of age can often result in occult gastrointestinal bleeding and IDA. Evidence was accumulating proving that early introduction cow milk (before one year of age) was a major factor responsible for the high prevalence rate of ID and IDA in infants.

AMERICAN ACADEMY OF PEDIATRICS COMMITTEE ON NUTRITION

The Committee on Nutrition (CON) of the American Academy of Pediatrics (AAP) in 1984 [12] set forth recommendations on diet and its effects on the health of children. Perusal of Table 2 will illustrate the temporal shift in feeding philosophy and CON
<table>
<thead>
<tr>
<th>CON/AAP</th>
<th>Recommendations</th>
<th>Future research</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>No convincing that feeding whole cow milk after 6 months of age is harmful</td>
<td>Maturation of infant gastrointestinal mucosal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amount and bioavailability of iron in diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can iron-fortified cereal meet an infant’s iron demands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does cow milk introduced at 6 months cause anemia and blood loss</td>
</tr>
<tr>
<td>1992</td>
<td>Whole cow milk should start at 12 months Discourage use of low iron-fortified formulas</td>
<td>Understand the implications of ID to brain dysfunction</td>
</tr>
<tr>
<td>1999</td>
<td>Human milk is preferred feeding for all infants Iron-fortified formulas for those not or partially breast fed Manufacture of low iron-fortified (&lt;= 4 mg/L) should cease Role of iron in infant growth and cognitive development Exclusively or partially breast fed require supplemental iron</td>
<td>Scientific update of previous CON/AAP statements</td>
</tr>
<tr>
<td>2010</td>
<td>Infants 6 to 12 months require 11 mg/day of iron Toddlers 1 to 3 years require 7 mg/day of iron Preterm infants through 12 months require 2 mg/kg of iron Screening for anemia and risk factors for ID/IDA at 12 months</td>
<td>Simplification of laboratory diagnosis of ID/IDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overcome barriers to iron supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reminders for screening and follow-up of children with ID/IDA</td>
</tr>
</tbody>
</table>

recommendations on how to best prevent ID. The 1984 statement proclaims that “there was no convincing evidence from well-designed research studies that feeding whole cow’s milk after 6 months of age is harmful if adequate supplementary feedings are given.”

In 1992, the CON recommended that cow milk should not be introduced into infants’ diet before 12 months of age [13]. These recommendations were based on cow milk-related enteric blood loss and inadequate bioavailability of electrolytic iron supplementing infant cereals [14, 15]. The next important step in helping to reduce the prevalence of I.D. in infants occurred in 1999, when the CON of the AAP [16] wrote that there was no role for the use of low iron-fortified formulas in infant feeding. Of interest to younger readers is that prior to and during this period, low iron-fortified formulas were more popular than iron fortified formulas. It was common practice for both pediatricians and parents to blame iron fortified formulas for any gastrointestinal symptom, especially constipation.

In 2007, the local Chapter 2 District II CON of the AAP endorsed the following recommendation: “In order to prevent ID and to reduce lead absorption all toddlers should be placed on daily supplemental iron (10 mg of elemental iron) at the time they are switched to regular cow’s milk. This may be given via a standard iron fortified vitamin and continued to age three.” Responding to a follow-up questionnaire 86% of the responding pediatricians agreed with this recommendation.

The 2010 report of the CON of the AAP [17] revisits the current ongoing problem of ID and IDA in infants and toddlers. This report has generated considerable
Iron Deficiency in the United States

TABLE 3 Prevalence of Iron Deficiency/Iron Deficiency Anemia in Toddlers

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Methods</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>24,894</td>
<td>Erythrocyte protoporphyrin, ferritin, transferrin saturation, and low hemoglobin</td>
<td>ID–9%, IDA–3%</td>
</tr>
<tr>
<td>21</td>
<td>504</td>
<td>Erythrocyte protoporphyrin, ferritin, lead, and hemoglobin</td>
<td>ID–7%, IDA1–0%</td>
</tr>
<tr>
<td>22</td>
<td>210</td>
<td>Reticulocyte hemoglobin, hemoglobin, iron, transferrin, transferrin saturation, circulating transferrin receptor, and ferritin</td>
<td>ID–20.5%</td>
</tr>
<tr>
<td>23</td>
<td>282</td>
<td>Hemoglobin, ferritin, and questionnaire</td>
<td>ID–7%, IDA–8%</td>
</tr>
</tbody>
</table>

ID - iron deficiency; IDA - iron deficiency anemia

Interest and controversy, and points out that IDA remains the major cause of anemia in young children. It states that ID even without anemia can adversely affect long-term neurodevelopment and behavior and the damage may be irreversible. The report advises universal screening for IDA at 12 months of age. Moreover, “high risk” patients (history of prematurity, low birth weight, exposure to lead, exclusive breastfeeding beyond 4 months of age without iron supplementation, feeding problems, poor growth, and low socioeconomic status) should also undergo screening. It is estimated that this “high risk” population represents over 50% of the total. However, normal hemoglobin values at one year of age do not protect infants from developing ID during the second year of life and the 2003–2004 5th edition of the AAP Pediatric Nutrition Handbook [18] states “ID and IDA continue to be a problem in the second year of life with an IDA prevalence of 10%.” Moser et al. [19] evaluated the incidence of developing IDA in the second year of life in infants who were non-anemic at 1 year of age on routine screening. Eighteen infants (9.3%) developed IDA and Jewish infants were more likely to be so diagnosed (13.3% versus 6.8%, P < 0.01).

PREVALENCE OF ID AND IDA

Due to the withholding of cow milk until 1 year of age, the use of only iron fortified formulas, and increasing breast feeding rates there has been a dramatic decrease in the prevalence of ID and IDA in infants as compared to the 1980’s. This remarkable public health achievement in lowering the prevalence of ID and IDA during infancy has not held true for toddlers ages one to three. Prevalence rates vary considerably from study to study. The widely quoted Third Nutrition Heath and Nutrition Survey (NHANES) conducted between 1988–1994 studied 24,894 persons one year of age and older [20]. These investigators reported a 3% prevalence of IDA and a 9% prevalence of ID in toddlers 1 to 2 years of age and showed that daily iron intake of 1 to 2 years olds was lower than in any other age group throughout life. These rates were slightly higher in adolescent girls and women of childbearing age. Table 3 shows the prevalence rates of ID and IDA in other studies [21–23].

ID AND LEAD TOXICITY

In 1999, a number of studies [24–26] demonstrated for the first time the association between ID and increased lead absorption. Contemporaneously, the iron transporter, DMT1, was identified and its function elucidated [27]. DMT1 transfers iron and other cations including lead across the apical surface of intestinal cells. Bradman et al. [24]
compared blood lead levels of iron-replete and iron-deficient children ($n = 319$ ages 1 to 5 years) residing in low, medium, or highly contaminated environments. Blood lead levels were higher for iron-deficient children. Wright et al. [25, 26] studied the association of ID and low-level lead toxicity and subsequent lead poisoning. In the first study [25], data was collected from 3650 children ages 9 to 48 months. The odds ratios for ID predicting lead levels greater than or equal to 5 and 10 $\mu$g/dL were 1.63 and 1.44, respectively, confirming the association between ID and low-level lead toxicity. The second study ($n = 1275$) [26] sought to determine whether ID is longitudinally associated with lead toxicity. This study concluded that ID is associated with subsequent lead poisoning.

**IRON THERAPY AND COMPLIANCE**

We will briefly discuss iron therapy concentrating on the problem of compliance, a major hurdle in the successful management of ID and IDA. For a more detailed review on iron therapy the interested reader can peruse Sandoval et al. [28] Studies using different iron preparations [29] or route of administration [30] have not resulted in improved compliance rates. Intravenous iron may become the preferred route of iron administration [31, 32]. Although insufficient data exist to brand intravenous iron as the new standard of care, newer intravenous iron preparations (ferumoxytol, ferric carboxymaltose, and iron isomaltoside) may allow complete replacement dosing with one infusion and minimal toxicity.

**CONCLUSION**

ID and IDA continue to pose public health challenges to pediatricians and patients alike. Current CON/AAP guidelines are paramount in preventing ID/IDA in toddlers. Dietary advice in the form of oral iron supplementation and limiting cow milk consumption may further reduce the incidence of ID/IDA. Indeed, we firmly believe that all children should receive supplemental iron once weaned off iron-fortified formula. We understand that no strategy is perfect and that compliance will always be the bane of our existence but we will continue our efforts on the front-line to prevent ID.

**Declaration of Interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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