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Iron deficiency increases blood concentrations of neurotoxic metals in children

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Iron deficiency affects approximately one-third of the world's population, occurring most frequently in children aged 6 months to 3 years. Mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese, lead, and cadmium, and a diet deficient in iron can lead to excess absorption of manganese, lead, and cadmium. Iron deficiency may lead to cognitive impairments resulting from the deficiency itself or from increased metal concentrations caused by the deficiency. Iron deficiency combined with increased manganese or lead concentrations may further affect neurodevelopment. We recently showed that blood manganese and lead concentrations are elevated among iron-deficient infants. Increased blood manganese and lead levels are likely associated with prolonged breast-feeding, which is also a risk factor for iron deficiency. Thus, babies who are breast-fed for prolonged periods should be given plain, iron-fortified cereals or other good sources of dietary iron.

Key words: Iron, Deficiency, Manganese, Lead, Breast-feeding

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Introduction

Iron deficiency, which is the most frequent and widespread nutritional deficiency in the world, affects approximately one-third of the world's population[1], and occurs most frequently in rapidly growing children aged 6 months to 3 years who have an inadequate dietary iron intake[2]. Iron deficiency is the only micronutrient deficiency that is also prevalent in virtually all developed countries[3]. The United States (US) National Health and Nutrition Examination Surveys (NHANES) 2003–2006 found that 14.4% of children aged 1–2 years were iron deficient[4]. To this end, one of the US national health objectives for 2010 was to reduce iron deficiency by 5%–9% in vulnerable populations, such as toddlers aged 1–2 years and pregnant women[5].

Many cross-sectional studies have found that iron-deficiency anemia (or other indications of chronic severe iron deficiency) in infancy is associated with poor cognitive development, poor motor development, and behavioral problems[6,7]. Longitudinal studies find persisting differences in cognitive development among children with iron deficiency[8,9]. Most studies report lower scores despite iron treatment and correction of anemia[7,10,11].

Prolonged breast-feeding, which is a risk factor for iron deficiency in infants, is associated with increased blood manganese and lead levels[12,13]. Infants breast-fed over a prolonged period tend to be iron deficient, and thus have higher blood levels of other metals. However, not all infants who are breast-fed for an extended period are iron deficient. This may be due to variations in the iron status of infants depending on whether they are provided with iron-rich food during the prolonged breast-feeding.

Inhalation of metals, such as manganese, lead, and cadmium, is the most common cause of adult toxic metal exposure in environmental and occupational settings[14], whereas food intake is the major source of absorbed metals in neonates and infants, who are more vulnerable than adults to metals absorbed through the intestine[15]. Mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese, lead, and cadmium[16,17], and a diet deficient in iron can lead to excess absorption of manganese[12,18-20], lead[13,21,22], and cadmium[23-25]. The gastrointestinal absorption of such divalent metals appears to involve intestinal iron transporters, such as apical divalent metal transporter 1 (DMT1)[16], which also mediates the uptake of the divalent metals[26]. Expression of DMT1 is up regulated in the presence of low iron stores[27], explaining the increased metal uptake[19,20,28] and higher blood concentrations of metals in iron-deficient individuals. Among divalent metals, both manganese and lead may adversely affect neurodevelopment in children[29]. Iron deficiency in children may affect cognitive impairment, resulting from the deficiency itself or from the increased metal concentrations caused by the iron deficiency. Therefore, iron deficiency combined with increased manganese or lead concentrations may further affect neurodevelopment.

Manganese

Manganese is a naturally occurring element abundant in the environment and is an essential dietary nutrient for humans. Because manganese is an essential element, its absorption, disposition, and biliary excretion are actively controlled by homeostatic mechanisms to maintain specific concentrations. These processes also play an important role in manganese toxicokinetics, which differ from those of nonessential, toxic metals such as lead and cadmium. Over-exposure to manganese can cause a neurologic impairment clinically known as "manganism," a motor syndrome similar to, but differentiated from, idiopathic Parkinson disease[30-33]. Recent epidemiological evidence suggests that low-level environmental exposure to manganese may adversely affect neurodevelopment in children[29]. Claus Henn et al.[34] found an inverted U-shaped relationship between blood manganese concentrations and neurodevelopment in 12-month-old infants, with both manganese deficiency and manganese excess associated with lower scores. In a study conducted in Quebec, children aged 6 to 13 years who had been exposed to drinking water containing elevated levels of manganese had significantly lower intelligence quotient (IQ) scores, with a 6.2-point difference observed between children in the highest vs. lowest manganese quintiles[35]. Manganese exposure has also been associated with an increased risk of hyperactive behavior problems[36,37].

Inhalation of manganese is the most common environmental cause of manganism[14]. Another source is the presence of a portal systemic shunt due to liver cirrhosis or portal vein thrombosis, which prevents the clearance of manganese via biliary excretion[38-40]. Animal and human studies have also demonstrated that iron deficiency markedly enhances intestinal absorption of manganese[18,28,41]. Iron shares similar absorption mechanisms with essential divalent metals, particularly manganese[16]. Thus, a diet deficient in iron can lead to excess absorption of manganese; therefore, iron deficiency can be a risk factor for the subsequent accumulation of manganese in the central nervous system[42-44].

Previous studies have shown that iron deficiency increases blood manganese concentrations in adults as well[20,28,41,45]. However, only a small number of case studies have examined the effect of iron deficiency on blood manganese levels in infants and children[46,47]. We, too, recently showed that blood manganese levels are elevated among iron-deficient infants[12]. Iron-manganese interactions underlie gender differences in blood manganese concentrations at different life stages. There are no gender differences in blood manganese concentrations before menarche, but blood manganese concentrations become higher in postpubertal women who have lower ferritin concentrations due to menstruation[20,48]. Moreover, blood manganese levels become lower after menopause due to correspondingly higher ferritin concentrations[49].

Lead

Lead is a widespread environmental pollutant that can damage the central nervous, renal, cardiovascular, reproductive, and hematological systems. Recently, new evidence of adverse central nervous effects at increasingly low levels of exposure is rapidly published. Blood lead concentrations significantly below 10 µg/dL are associated with negative outcomes such as reduced IQ, executive function deficits, and attention deficit hyperactivity disorder[29]. One of the more notable recent findings is that the slope of the dose-effect relationship between blood lead concentration and neurodevelopment is not linear, but rather supralinear, such that the rate of decline in children's IQ scores is greater at blood lead levels below 10 µg/dL than at levels greater than 10 µg/dL. In early 2012, the US Centers for Disease Control (US CDC) concluded that a blood lead concentration of 5 µg/dL places a woman's fetus at increased risk of adverse effects and warrants follow-up testing, patient education, and nutritional, environmental, and behavioral interventions to reduce lead exposure[29]. Also in 2012, the US CDC abandoned use of the term "level of concern" regarding childhood lead poisoning, citing a lack of evidence that any blood lead level can be considered "safe"[50].

Several previous studies have assessed the temporal relationship between iron deficiency and increased blood lead concentrations[13,21,51,52]. A longitudinal study showed an association between iron deficiency and high blood lead levels in young children, with blood lead levels ranging from <5 µg/dL to 40 µg/dL[52]. In another study of children aged 10–15 years, the mean blood lead concentration was found to be 6.9 µg/dL in iron-deficient children and 4.3 µg/dL in normal children, and that iron supplementation significantly decreased blood lead concentrations in the former group[21]. A clinical trial assessing the impact of iron supplementation on blood lead concentrations in infants with iron deficiency found that changes in blood lead concentrations corresponded closely with changes in iron status[13,51]. In contrast to the studies described above, others have found no association between iron deficiency and increased blood lead concentrations[53-59]. This discrepancy may be due in part to differences in the age distribution of the study subjects, the assumptions used, or the degrees of lead exposure. For example, no association was observed in studies where the subjects were older female children or adolescents[53,55,60]. In postmenarche women, estrogen promotes bone mineralization and redistributes blood lead into bone; thus, women have lower blood lead concentrations than men and there is no association between high blood lead levels and iron deficiency in postmenarche adolescents owing to the overshadowing effects of estrogen on lead levels[61]. Some studies of children with lower blood lead concentrations (11.0 µg/dL and 11.4 µg/dL) have reported no association[54,58]. However, longitudinal studies of children with blood lead levels in a similar range have shown an association between iron status and blood lead concentration in children following iron supplementation[21,51,52]. Furthermore, we recently observed an association between iron supplementation and blood lead levels in infants with very low blood lead concentrations (1.416–1.846 µg/dL)[13]. Such minor increases in blood lead concentrations due to iron deficiency may have toxicological implications in children, considering the lack of evidence that any level of lead in the blood can be considered "safe."

Cadmium

Cadmium is a ubiquitous environmental pollutant with a biological half-life in the body exceeding 10 years. Cadmium levels in the body accumulate with age, since only a minute part of the body burden (0.01%–0.02%) is excreted per day[62]. Cadmium has been reported to have cumulative effects on mortality and cardiovascular, renal, and developmental diseases[62], and blood cadmium concentration is a valid biomarker of recent cadmium exposure[63]. Cadmium levels have been reported to increase as iron stores decrease in premenopausal women[48,53,64-70]. However, no association between iron deficiency and elevated cadmium levels has been observed in postmenopausal women[71-73] or in men[70,74], and few studies to date have analyzed the association between iron deficiency and elevated cadmium levels in children[53]. Furthermore, the studies performed in children have yielded conflicting results. Some studies reported an association between iron deficiency and cadmium[75,76], whereas others found no such association[77,78], and one study reported only an association between ferritin and cadmium concentrations in female adolescents[53]. Our recent study showed no association between iron deficiency and cadmium concentration in infants[79]. In contrast, assessment of the same study subjects showed that iron deficiency was associated with increased blood lead and manganese concentrations[12,13]. Our finding that iron deficiency and blood cadmium levels in infants are not related[79] is compatible with some previous studies in children[77,78] but not with others[75,76]. These discrepancies may be partly owing to differences in cadmium exposure levels or to the age distribution of study participants. For example, the two studies that found an association between iron deficiency and cadmium levels documented children living in an heavily air-polluted area of Turkey[75] and children with blood cadmium concentrations more than 7 folds higher than those in our previous study[76]. The study subjects in our previous study were infants living in a nonpolluted area who had very low blood cadmium concentrations. Furthermore, most previous studies included children and/or adolescents as study subjects, but not infants[53,75-78].

The placenta may act as a partial barrier to fetal exposure to cadmium[80], and only 5%–10% of maternal blood cadmium is transferred to human milk owing to metallothionein binding of cadmium in blood cells[81]. Cadmium concentrations tend to increase with age[62,74,82,83]. Thus, the likelihood of exposure to cadmium may be reduced in infants and they may not show elevated blood cadmium levels associated with iron deficiency. In contrast, lead is more abundant than cadmium in sources to which infants may be exposed, thus lead is more often absorbed by infants with iron deficiency[13]. Manganese is abundant in foods as an essential element, and is also easily absorbed in subjects with iron deficiency[20,29,32,33].

Conclusions

First, the data summarized here emphasize the importance of assessing iron and hematologic status in children when addressing environmental exposure to neurotoxic metals, such as manganese and lead, and related neurobehavioral effects. Given the high prevalence of iron deficiency in children, the

epidemiology of iron deficiency should be studied to assess its role as an important susceptibility factor, especially when carrying out environmental health risk assessments concerning low exposure to neurotoxic metals in children. Second, these findings indicate the possible role of exposure to neurotoxic metals in aggravating iron-related developmental and behavioral problems in children. Third, increased blood manganese and lead concentrations are probably associated with prolonged breast-feeding, which is also a risk factor for iron deficiency. Thus, babies who are breast-fed for prolonged periods should be given plain, iron-fortified cereals, or other good sources of dietary iron.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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