Zinc deficiency and child development[1–3]

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ABSTRACT Zinc is a trace metal that is present in the brain and contributes to its structure and function. Limited evidence from both animal and human studies suggests that zinc deficiency may lead to delays in cognitive development. Although the mechanisms linking zinc deficiency with cognitive development are unclear, it appears that zinc deficiency may lead to deficits in children's neuropsychologic functioning, activity, or motor development, and thus interfere with cognitive performance. In this article a model is presented that incorporates the influence of social context and the caregiving environment and suggests that the relation between zinc deficiency and cognitive development may vary by age in children and may be mediated by neuropsychologic functioning, activity, and motor development. Suggestions for further research are provided. *Am J Clin Nutr* 1998;68(suppl):464S–9S.

KEY WORDS Zinc deficiency, cognitive development, motor development, activity, attention, neuropsychologic function, children

ZINC DEFICIENCY AND CHILD DEVELOPMENT

Nutritional deprivation is a serious international problem that can lead to long-term deficits in growth, immune function, cognitive and motor development, behavior, and academic performance. Although in the past most of the attention has been directed toward the negative consequences associated with inadequate protein-energy intake, there is increasing recognition of the important role that micronutrient deficiency plays in children's cognitive and motor development. For example, deficiencies in iron and iodine have been directly linked with cognitive and motor delay (1, 2). Recent evidence also suggests that zinc deficiency may be associated with deficits in activity, attention, and motor development that commonly occur in nutritionally deficient children.

Zinc is a trace mineral that plays a central role in cellular growth, specifically in the production of enzymes necessary for the synthesis of RNA and DNA (3, 4). Zinc is prevalent in the brain, where it binds with proteins, thus contributing to both the structure and function of the brain (5, 6). Severe zinc deficiency in animals has been associated with structural malformations of the brain, such as anencephaly, microcephaly, and hydrocephaly (7); with behavioral problems, such as reduced activity (8) and deficits in short-term memory and spatial learning (9). In humans, severe zinc deficiency can cause abnormal cerebellar function and impair behavioral and emotional responses (10, 11). This paper will examine the evidence linking mild-to-moderate zinc deficiency with children's cognitive development.

Age may be important to consider in the link between zinc deficiency and children's cognitive development because children may be particularly vulnerable to zinc deficiency during periods of rapid growth and development, such as infancy and adolescence. Inner-city children from low-income families were found to have low concentrations of plasma zinc during infancy and adolescence (12), and dietary reports from middle-income families suggest moderate zinc deficiency during infancy (13). In addition, the potential link between zinc deficiency and cognitive development may be stronger in children at risk for deficits in cognitive and motor functioning, such as children who are born prematurely, who have nutritional problems, and who have chronic diseases that interfere with absorption or growth.

COGNITIVE AND MOTOR DEVELOPMENT

Undernourished children often have deficient or delayed cognitive and motor development (14–16). However, nutritional deficiency often occurs in the context of poverty and deficient caregiving behavior (17). Because poverty itself has been associated with deficits in cognitive and motor performance (18), the etiology of the developmental problems common in undernourished children often includes contributions of both nutritional and environmental factors (17, 19). Regardless of the origin, the consequences of early developmental problems in children can be long lasting and compromise academic performance and the ability to contribute to society.

Early developmental performance predicts subsequent performance as children practice and master emerging skills and ready themselves for the acquisition of new skills. Bertenthal and Campos (20) demonstrated how locomotor skills such as crawling provide children with increasing independence. Children who are mobile or able to change their position can direct their attention to a wide array of social and physical components of their environment with less dependence on caregivers. In turn, children's emerging mobility elicits a new array of responses from caregivers. Although zinc nutriture has been implicated as

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an important factor in children's activity, attention, and development, there is no clear explanation of the mechanisms underlying the relation.

ACTIVITY

Nutritionally deprived children are frequently described as lethargic, possibly because they reduce their activity as a protective strategy to conserve energy (21). Yet reduced activity may have negative consequences for children's motor and cognitive development (22). Children who are inactive and do not practice their existing skills may be less likely to acquire new or more complex skills (23, 24).

Activity is a complex construct because it increases during infancy as children gain motor skills and then decreases during the preschool period as children focus their attention on specific objects or events (25). In addition, the quality of children's activity changes during early childhood. Belsky and Most (26) demonstrated the developmental sequences of activity and exploration that occur between 7 and 21 mo of age in healthy children. Using activities and materials within the children's developmental level, they noted that older toddlers spent less time in undifferentiated activities (eg, mouthing, banging, and shaking) and more time in functional and relational activities (eg, visually guided manipulation and combining 2 objects). Thus, the links between activity and development may include attention and exploration. As children attend to objects and explore their functional and relational properties, they gather and organize information, building structures that enhance cognitive development (27).

ATTENTION

From birth, infants are confronted with massive amounts of information from multiple sources. They learn to differentiate relevant from irrelevant information so they can focus their attention on the information necessary for their growth and development. Most assessments of early attention focus on visual attention or the length of time infants gaze at an object or event. During focused attention infants inhibit other activities, such as extraneous movements or talking, and they are not easily distracted by external stimuli. Ruff and Rothbart (28) describe the development of attention as involving 2 systems. The orientation-investigative system is active during the first year of life as infants explore novel aspects of their environment. Early exploration is partially dependent on developmental skills and activity. For example, an undernourished child who has delayed motor skills or is lethargic has fewer opportunities for exploration than does the child with better motor skills who is more active and seeks opportunities for exploration. Exploration is often reinforcing to infants and provides them with information about their environment that enhances their development.

The second system of attention begins at the end of the first year of life and develops during the preschool years. It extends beyond orientation and investigation to include more sophisticated functions such as planning, testing, and organizing information. As memory and language skills become more developed, attention emerges as a critical component in learning. However, attention often demands the suspension of activity, particularly undifferentiated or irrelevant activity, so the child can concentrate on a specific object or event. This system of attention corresponds to the decrease in undifferentiated activity and to the increase in functional and relational activity described by Belsky and Most (26).

SOCIAL CONTEXT

Social context is a critical component of infant development that was not always considered in investigations of nutrition and development (17). Not only do infants depend on families for nutrients and basic care, but their early behavior and development is influenced by the responsivity of the caregiving environment, particularly interactions with their primary caregiver (29). The presence of the primary caretaker influences the play behavior of young children, such that children are more active in their mother's presence than in her absence (30). Maternal affect is also an important component of children's early development. Maternal depression has been associated with cognitive and emotional problems in children (31, 32), and infants raised in non-nurturant or neglecting families are more likely to develop insecure, anxious attachments (33, 34). In addition, the demands of the caregiving situation can influence children's behavior. For example, infants and toddlers are observed to be more interactive and more negative with their caregiver during feeding than during free play, perhaps because feeding is a relatively structured activity with clear demand characteristics, whereas in a free play setting children are encouraged to explore and become involved with the materials (35). Current models of child development highlight the interactive influences of the social context, including families and the surrounding environment, on children's development (36).

ZINC DEFICIENCY AND DEVELOPMENT

Animal Research

Most animal models of the effects of zinc deprivation on activity, attention, and development have been conducted in rats and monkeys. Rats have generally been used to examine the effects of deprivation during the prenatal or infancy periods, and monkeys have served as models for deprivation during infancy, childhood, or adolescence. Monkeys are ideal animal models for investigations of childhood zinc deprivation because the period between the end of weaning and the onset of puberty (eg, childhood) extends for 3 y, as opposed to only 2 wk in rats.

Halas et al (9) examined zinc deficiency in rats during the infancy period by depriving the animals of zinc during early development, refeeding them, and examining their behavior as adults. Early severe zinc deficiency led to increased emotionality in adults (eg, response to stress).

Golub (37–40) examined the effect of zinc deprivation on the behavior and development of young rhesus monkeys using a procedure in which well-nourished juvenile monkeys were fed a zinc-deficient diet, thus simulating zinc deficiency during childhood. Short-term (15 wk), moderate zinc deprivation in prepubertal monkeys resulted in reduced motor activity and less accurate performance on measures of attention and short-term memory (38).

In an investigation of long-term, moderate zinc deficiency in primates initiated during the prepubertal period and extending through puberty (18–33 mo of age), differences in activity preceded differences in growth and plasma zinc concentrations (40). Specifically, zinc deficiency was associated with decreased

activity and accuracy related to inhibitory control (measured by accuracy on a continuous performance task), but only during the premenarcheal period (40). During the postmenarcheal period there were no differences in activity or inhibitory control related to zinc deprivation. In contrast, monkeys in the zinc deprivation group did not experience reduced growth rates or lower concentrations of plasma zinc until they entered their growth spurt (27–33 mo of life). Thereafter, zinc-deficient monkeys had lower rates of growth and plasma zinc concentrations than did adequately nourished monkeys. The finding that diminished activity and inhibitory control occurred before changes in growth and plasma zinc concentrations suggests that animals may have been conserving energy or control in response to zinc deprivation. There was no effect of zinc deprivation on a measure of attention, but the testing periods were relatively brief and may not have adequately assessed sustained attention.

Studies of severe zinc deprivation in monkeys before weaning showed that zinc-deficient animals were emotionally less mature, as demonstrated by their difficulty with separation and the increased protective behavior by their mothers (41). There were also cognitive deficits associated with severe zinc deprivation in juvenile monkeys (those who had been weaned), indicated by their difficulty in retaining previously learned visual discrimination problems and difficulty learning new problems.

Human research

Most human studies of zinc deficiency were conducted in vulnerable or nutritionally deprived children. For example, Friel et al (5) enrolled 52 infants (41 appropriate-for-gestational age, 11 small-for-gestational age) with birth weights <1500 g. Through a randomization procedure that occurred at hospital discharge, half received a zinc-enhanced supplementation of 11 mg Zn/L and 0.9 mg Cu/L and half received a supplementation of 6.7 mg Zn/L and 0.6 mg Cu/L (copper was added because zinc may inhibit its absorption). Supplementation continued for 5 mo and children were evaluated on the Griffiths mental development scales (42, 43) at 3, 6, 9, and 12 mo of age. Plasma zinc concentrations were higher for the infants in the zinc-enhanced supplementation at discharge and 3 mo, but not at 6, 9, or 12 mo when the infants were no longer receiving zinc-enhanced supplementation. Results did not differ by the initial size-for-gestational age of the very-low-birth-weight infants. Infants who received the zinc-enhanced supplement had a greater linear growth over the entire study period than did infants in the comparison group, although there were no differences in the growth velocities of weight or head circumference. Subsequent analyses showed that the beneficial effects of supplemental zinc on linear growth were experienced by girls but not boys. When development was considered over the study period, there were no differences in total Griffiths scores, but children in the zinc-enhanced supplementation group had better scores in motor development.

One study examined the link between maternal sources of zinc and infant development in a subset of Egyptian mothers and infants and found that micronutrient intake during the second and third trimesters of pregnancy, including bioavailable zinc (based on self-report of zinc from animal sources) was related to the habituation cluster of the Brazelton Neonatal Behavioral Assessment Scale administered shortly after birth (44, 45). Habituation is an early measure of attention in which success is based on the infant's ability to differentiate familiar from novel stimuli and then to inhibit responding. When the Bayley Scales of Infant Development (46) were administered at 6 mo of age, motor development was negatively related to maternal intake of plant zinc, fiber, and phytate, probably related to their low bioavailability. That is, children of mothers with high intakes of plant zinc through the lactation period (as opposed to animal zinc) were likely to have low scores on motor development. In addition, motor development was lower in infants with frequent diarrhea and higher in infants with more household economic resources. These findings showed the multiple effect of maternal nutrition and psychosocial risk on development.

Two studies used zinc supplementation trials to examine the relation between zinc deprivation and activity in undernourished infants and toddlers (47, 48). In the trial conducted in India, children 6–35 mo of age were recruited from a low-income community when they presented with diarrhea (47). None of the children were severely malnourished, but approximately half were stunted, wasted, or both. The children were randomly assigned into zinc-supplemented or control groups. The children in both groups received a liquid preparation of niacinamide and vitamins A, B-1, B-2, B-6, D_3, and E daily for 6 mo. In addition, the preparation for the children in the zinc supplementation group contained 10 mg elemental Zn (47). After a 2-d evaluation, infants in the zinc-supplemented group were observed to be more likely to engage in high movement activities (eg, running) than infants who did not receive zinc, with greater effects in boys. The Guatemalan trial involved infants recruited at 6–9 mo of age (48). The children were randomly assigned to a zinc-supplemented group that was given 10 mg oral Zn/d for 7 mo or to a control group. Both groups were evaluated through observation at 3 and 7 mo after baseline. There were no differences when children were rated by the motor developmental milestones they demonstrated during 3- or 7-mo observations, but at the 7-mo follow-up infants in the zinc-supplemented group were more likely to sit, rather than lie down, and to play. Taken together, these 2 studies suggest that zinc nutriture may play an important role in the development of motor skills in young children.

Although research conducted through the preschool years suggests that zinc may be important in children's early development, the evidence from studies in school-age children is controversial (49–51). In a cross-sectional study conducted in school-age, stunted children [age 81.5 ± 7.0 mo ($\bar{x}$ ± SD)] in Guatemala, low hair zinc (<1.68 μmol/g) was associated with increased weight-for-age, increased weight-for-height, and decreased taste acuity (49). Low plasma zinc was associated with decreased height-for-age. Thus, zinc-deficient children tended to be somewhat short and heavy. However, there were no differences in attention span [measured by subtests of the Detroit Tests of Learning Aptitudes (52)] based on zinc status. Boys were more likely to have low zinc status (measured by both hair and plasma) than were girls.

In Canada, a zinc supplementation trial was conducted in stunted school-age boys 5–7 y of age (50). The boys were randomly assigned into zinc-supplemented or placebo groups. Children in the zinc-supplemented group received 10 mg Zn/d for 12 mo. At the end of the study when the data were analyzed by treatment group, there were no differences in growth, biochemical indexes, taste acuity, or attention span (measured by 4 subtests from the Detroit Tests of Learning Abilities). However, initial zinc status moderated the effects of supplementation on growth. When the data were analyzed by the children's initial hair zinc concentrations (< or >1.68 μmol/g), the boys in the low-zinc

group who received supplementation had a higher mean change in height-for-age *z*-score than did the boys in the other 3 groups. Although there were no differences in taste acuity, energy intake, or attention span related to supplementation, boys in the low-zinc group had a lower mean weight-for-age and were less sensitive to the taste acuity test at baseline. These data suggest that not only is zinc deficiency associated with compromised growth and taste acuity of school-age boys, but zinc supplementation is only effective in remediating linear growth in stunted boys with low hair zinc concentrations. Taken together, these studies suggest that in school-age, stunted children, those with zinc deficiency are smaller, and boys may be more vulnerable to zinc deficiency than girls. However, zinc deficiency was not related to standardized measures of cognitive functioning and attention.

At least 1 study showed a relation between zinc supplementation and performance in school-age children. In a recent evaluation of 372 first-grade children (ages 6–9) from low income families in China, children who received supplementary zinc with or without other micronutrients for 10 wk functioned better on a battery of neuropsychologic tests than did those who received micronutrients only (51). Thus, there is some evidence suggesting that zinc is an essential mineral for neuropsychologic functioning during childhood.

DISCUSSION

From the animal literature it appears that zinc deficiency may undermine cognitive and motor development through associations with decreased activity and perhaps with emotionality. Evidence from the human literature is less clear. The most striking evidence has emerged from the studies conducted during infancy. Low maternal zinc nutriture has been associated with less attention during the neonatal period (44) and worse motor functioning at 6 mo of age (40), and zinc supplementation has been associated with better motor development in very-low-birth-weight infants (5), more vigorous activity in Indian infants and toddlers (47), and more functional activity in Guatemalan infants and toddlers (48). Zinc supplementation was associated with better neuropsychologic functioning in first-grade students in China (51). However, there were no relations between zinc supplementation and measures of attention through standardized test performance in school-age, stunted children in a cross-sectional study in Guatemala (49) or a supplementation trial in Canada (50).

There are several possible explanations for these findings. First, as suggested by the animal studies, zinc deficiency may affect children's emotionality and response to stress, rather than cognitive performance per se. Thus, a zinc-deficient child may be particularly responsive to the social context and to environmental stress. For example, a child who is zinc deficient may have difficulty with maternal separation early in life. However, none of the human studies have examined this possibility.

Second, zinc deficiency may affect cognitive performance through alterations in attention, activity, and other aspects of neuropsychologic functioning, such as planning or inhibition. Although children with deficits in neuropsychologic functioning often have deficits in cognitive capabilities, children with attention deficit hyperactivity disorder may have cognitive capabilities in the normal range with specific deficits in neuropsychologic functioning. Thus, it may be possible for zinc-deficient children to demonstrate normal cognitive functioning, but still be impaired by deficits in neuropsychologic functioning that undermine academic performance.

A third possibility is that zinc deficiency leads to reduced levels of activity, which then inhibit the development of cognitive development. Depressed activity has been implicated in both animal and human research involving zinc deprivation. Although activity may be partially dependent on energy expenditure, there appear to be other factors associated with individual variations in activity that should be considered in assessments of activity in undernourished children. For example, in well-nourished children the relation between activity and development may be curvilinear, such that both high and low levels of activity are viewed with concern and are not associated with optimal development (26). Thus, children who are hyperactive and display high levels of undifferentiated activity may not achieve the cognitive and motor benefits that have been associated with functional and relational activity.

The link between motor development and activity is important to consider because children with delayed motor development may be less active merely because they lack the skills to demonstrate vigorous activity. In a recent investigation in stunted toddlers in Jamaica, investigators found that at baseline, stunted children were less active than nonstunted children (as observed in children's homes) and their level of activity was related to their performance on a standardized assessment of development (53). However, after 6 mo the level of activity had increased significantly in the stunted children regardless of whether they had received nutritional supplementation, psychosocial stimulation, or neither. The stunted children's level of activity did not differ from that of the nonstunted children and there was no longer a relation between activity and development. The increased activity may be explained by the children's increasing developmental skills. Many of the stunted children were unable to run at baseline, but all children could run at the 6-mo evaluation. Because activities defined as vigorous were dependent on children's locomotor abilities ("walk rapidly" and "run, skip, jump, hop"), the children's motor skills at baseline may have hindered their performance on the assessment of activity. Once they acquired the ability to run, there were no differences in activity. Thus, activity should be evaluated in reference to children's motor skills.

A fourth possibility is that contextual factors, such as maternal responsivity and developmental stimulation, may also play a role in the link between zinc status and development, as they do in the link between nutritional deprivation and development (54). However, none of the studies of zinc deprivation have examined the mitigating role that may be played by children's environment.

Finally, the relation between zinc deficiency and cognitive development in children may vary by age. One would expect the effect of zinc deprivation to be stronger during times of rapid growth, such as infancy. However, there have not been enough studies to evaluate the differential effect of zinc deficiency across childhood.

Taken together, these findings suggest a path model in which neuropsychologic functioning (eg, attention), activity, and motor development mediate the relation between zinc deficiency and cognitive development (**Figure 1**). Age is included as a potential moderator because the relation between zinc deficiency and cognitive development may vary by age. This model is consistent with the mechanisms linking nutrition and cognitive develop-

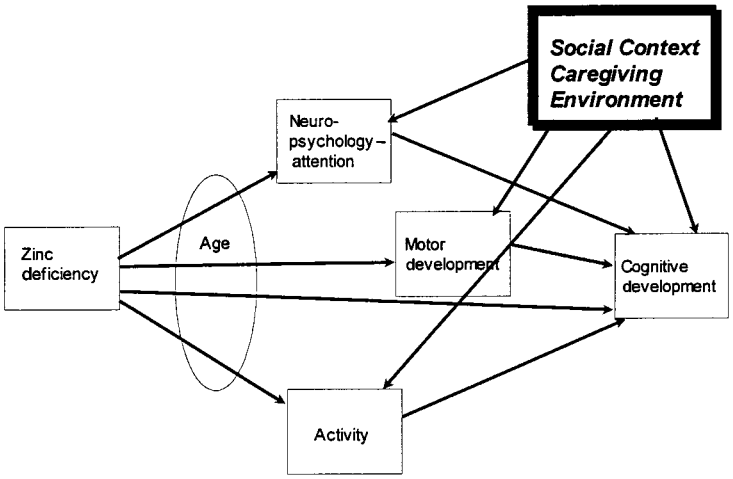

FIGURE 1. A path model linking zinc deficiency in children to cognitive development, moderated by age and mediated through neuropsychologic functioning, activity, and motor development.

ment proposed by Pollitt et al (19). Both models include the social context (eg, poverty) and the caregiving environment (eg, maternal and family functioning) as important determinants of children's development.

DIRECTIONS FOR FUTURE RESEARCH

Although the initial studies linking zinc deficiency and cognitive development in children suggest a relation in which cognitive development is depressed, perhaps through deficits in activity, attention, and motor development, much more research needs to be done in both animals and humans. Studies of infant development could include measures of maternal dietary intake during pregnancy and lactation, with attention to the bioavailability of sources of zinc (40). Maternal micronutrient deficiencies, particularly when they occur in combination with psychosocial risks, may undermine early infant development.

In addition to general indexes of developmental and academic performance, investigators should examine how neuropsychologic functioning may contribute to overall performance within a developmental context. During infancy, measures of activity and attention may be relevant. However, activity must be interpreted in reference to children's motor development, given the potential confound between activity and motor development. During the school-age years, it may be useful to measure other neuropsychologic measures that have been linked with zinc deficiency and may undermine cognitive performance in school settings, such as abstract reasoning, concept formation, motor tracking, visual perception, short-term visual memory, and continuous performance. Thus, the mediating effects of neuropsychologic functioning in the link between zinc deficiency and cognitive development may vary by children's age. In addition, investigators should include measures of social context and the caregiving environment, along with analyses to investigate the increased risk or protection they provide to the child.

Zinc deficiency often occurs in combination with other micronutrient deficiencies and the mechanisms linking zinc deficiency to cognitive development are unclear. Additional research is necessary to examine the effect of zinc supplementation in combination with other micronutrients. In addition, research is needed to examine the effect of alternative forms of acquiring zinc, such as food fortification, on cognitive development.

Sex differences have been found in several studies, suggesting that boys are more vulnerable to zinc deficiency than girls (47, 49). However, additional research is needed to clarify this finding and to examine the mechanisms underlying sex differences.

Without a clear index of zinc status, investigators rely on response to supplementation as an indication of zinc deficiency. However, the processes invoked in response to supplementation may not be the same as those activated by zinc deprivation. Thus, there is an ongoing need for animal research in which animals are differentially zinc-deprived without the complicating factors of a compromised social context and caregiving environment that often accompany zinc deprivation in nutritionally deprived children.

Finally, recent evidence that mild zinc deficiency may be widespread, even in populations that are adequately nourished (13), raises questions about the effect of zinc deprivation without the complicating factors of overall nutritional deprivation or poverty. Research that examines response to zinc supplementation (or fortification) in populations that are zinc deficient in the absence of poverty would help to clarify the relation between zinc deficiency and cognitive development. Thus, zinc deficiency may be a serious public health problem that compromises the development of millions of children in both developing and industrialized countries (55).

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