Overview of Inherited Zinc Deficiency in Infants and Children

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Summary  Zinc nutrition is of special practical importance in infants and children. Poor zinc absorption causes zinc deficiency, which leads to a broad range of consequences such as alopecia, diarrhea, skin lesions, taste disorders, loss of appetite, impaired immune function and neuropsychiatric changes and growth retardation, thus potentially threatening life in infants and children. In addition to dietary zinc deficiency, inherited zinc deficiency, which rarely occurs, is found during the infant stage and early childhood. Recent molecular genetic studies have identified responsible genes for two inherited zinc deficiency disorders, acrodermatitis enteropathica (AE) and transient neonatal zinc deficiency (TNZD), clarifying the pathological mechanisms. Both of these zinc deficiencies are caused by mutations of zinc transporters, although the mechanisms are completely different. AE is an autosomal recessive disorder caused by mutations of the ZIP4 gene, consequently resulting in defective absorption of zinc in the small intestine. In contrast, TNZD is a disorder caused by mutations of the ZnT2 gene, which results in low zinc breast milk in the mother, consequently causing zinc deficiency in the breast-fed infant. In both cases, zinc deficiency symptoms are ameliorated by a daily oral zinc supplementation for the patients. Zinc is definitely one of the key factors for the healthy growth of infants and children, and thus zinc nutrition should receive much attention.

Key Words  zinc deficiency, infants, children, acrodermatitis enteropathica, transient neonatal zinc deficiency

The optimal growth and development of infants and children requires a number of micronutrients. Zinc is one such micronutrient because it plays a pivotal role as a structural, catalytic, and signalling component within protein functions. Recent human proteomic analyses indicate that about 10% of proteins have been estimated to have the potential to bind zinc, which also reflects the indispensability of zinc for numerous physiological processes. In fact, zinc is essential for growth and development, immune, nervous system and endocrinial functions, and, in particular, is required during the first years of the life when the body is growing rapidly. Hence, in developing countries, where malnutrition is common, zinc deficiency is still a health problem; zinc deficiency increases the risk of morbidity and mortality of young children (1, 2). In these countries, zinc supplementation in infants and children can prevent and reduce the severity of common diseases such as diarrhea, lower respiratory tract infections, and improve linear growth velocity. In developed countries, zinc deficiency in infants and children is much less common (3).

Zinc deficiency in infants and children usually occurs through insufficient intake of dietary zinc, but it also rarely occurs in an inherited manner, which is diagnosed as acrodermatitis enteropathica (AE) or transient neonatal zinc deficiency (TNZD) (4). Recent genetic studies have indicated that these conditions can be caused by mutations in zinc transporter genes and have clarified the pathological mechanisms in patients. This paper reviews current knowledge of zinc deficiency in infants and children, emphasizing the molecular basis of hereditary zinc deficiency disorders, AE and TNZD, from the standpoint of functions of the responsible zinc transporters.

Requirement of Zinc for Optimal Growth of Infants and Children

Zinc in breast milk is bound to a number of different components including casein (14%), albumin (28%), low-molecular weight ligands (29%) and fat (29%) (5). Breast milk zinc concentrations, particularly in the first 3 mo, are considerably higher than those of the maternal serum, which reflects the infant’s requirement of a large amount of zinc for growth and development. Compared with full-term infants, preterm infants are in negative zinc balance at birth because of the lower capacity for gut absorption (6), and thus the demand for zinc increases rapidly in thriving preterm infants (7). Hence, the preterm infant has an increased risk of zinc deficiency and symptomatic zinc deficiency has been mostly found in breast-fed preterm infants (8). Zinc deficiency also rarely occurs in breast-fed, full-term infants, in which hereditary AE and TNZD are likely (see below).

Children also need large amounts of zinc for their rapid growth. Recommendations for zinc intake differ between males and females at the age of 15 y in most countries, but range from 2.9 to 10.0 mg/d in children aged 5 y, 5.7–15.5 mg/d (boys) and 4.6–15.0 mg/d...
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children between 6 mo and 5 y of age is attributable to that 4% of the global morbidity and mortality of young dietary needs for zinc may not be met. It is estimated oped countries. Conversely, zinc deficiency in children severe zinc deficiency to be much less common in devel-

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zinc deficiency (mutations of the Acrodermatitis Enteropathica and ZIP4 (SLC39A4) mutated to the cellular compartments (10). In these processes, zinc transporters play crucial roles. In general, zinc transporters are divided into two groups, solute carrier 30A (SLC30A) and SLC39A: SLC30A is named Zn transporter (ZnT) and SLC39A is named Zrt. Irt-like protein (ZIP) (10, 11). ZnT transporters export cytosolic zinc into the extracellular space or lumens of intracellular compartments, while ZIP transporters import zinc into the cytosol from the extracellular space or lumens of intracellular compartments. Most ZIP transporters have been shown to be localized in the plasma membrane, while most ZnT transporters are localized in the intracellular compartments. Zinc transporters have crucial functions in physiology and dysfunctions of these by mutations result in inherited diseases. Moreover, single nucleotide polymorphisms (SNPs) in both transporters related to pathologies of the diseases have been identified (4). Thus, the study of these zinc transporters is currently of great clinical interest. In zinc defi-

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ence in infants and children, AE (MIM No. 201100) and TNZD (MIM No. 608118) have been shown to be caused by mutations of ZIP and ZnT2 transporter genes ZIP4 and ZnT2, respectively (Table 1). In both cases, symptoms of zinc deficiency, including erythematous and erosive dermatitis, persistent diarrhea, hair loss, and transient growth retardation, are ameliorated by zinc supplementation.

Two Zinc Transporters, ZnT and ZIP

Zinc balance is primarily maintained through a regulated rate of intestinal absorption, and gastrointestinal secretion, renal excretion and sloughing of mucosal cells and integuments. After absorption, zinc is delivered to the peripheral tissues and cells, and then is distributed to the cellular compartments (10). In these processes, zinc transporters play crucial roles. In general, zinc transporters are divided into two groups, solute carrier 30A (SLC30A) and SLC39A: SLC30A is named Zn transporter (ZnT) and SLC39A is named Zrt. Irt-like protein (ZIP) (10, 11). ZnT transporters export cytosolic zinc into the extracellular space or lumens of intracellular compartments, while ZIP transporters import zinc into the cytosol from the extracellular space or lumens of intracellular compartments. Most ZIP transporters have been shown to be localized in the plasma membrane, while most ZnT transporters are localized in the intracellular compartments. Zinc transporters have crucial functions in physiology and dysfunctions of these by mutations result in inherited diseases. Moreover, single nucleotide polymorphisms (SNPs) in both transporters related to pathologies of the diseases have been identified (4). Thus, the study of these zinc transporters is currently of great clinical interest. In zinc defi-

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Acrodermatitis Enteropathica and ZIP4 (SLC39A4)

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quentley resulting in reduced intestinal zinc absorption. AE is characterized by eczematous dermatitis, alopecia and diarrhea, typically occurring in early infancy but also after weaning in breast-fed infants (12), with an estimated frequency of about 1 in 500,000 (13). The zinc deficiency symptoms in patients with AE disappear if daily oral zinc supplementation is administered (1–3 mg/kg/d of elemental zinc) (13). At present, a myriad of mutations, including missense, nonsense, deletion, insertion, or splice-site mutations in the ZIP4/SLC39A4 gene have been identified in AE patients (4) since the first reports of the mutations in 2002 (14, 15). Pathogenic mutations in AE have been shown to result in defects in zinc responsive trafficking to the plasma membrane, reduced zinc uptake activity (16), or defects in processing, in which the extracellular amino-terminal domain of ZIP4 undergoes proteolytic cleavage during extended periods of zinc deficiency (17). The molecular mechanism causing severe dermatitis, which is one of the primary features in AE patients and severe zinc deficiency, has been shown not to be attributable to allergic contact dermatitis, but irritant contact derma-

titis, which is caused by loss of Langerhans cells with a protective role against ATP-mediated inflammatory sig-
nals (18). However, those causing alopecia and diarrhea in AE patients remain unknown.

Transient Neonatal Zinc Deficiency and ZnT2 (SLC30A2)

Zinc deficiency also occurs in breast-fed, full-term infants, and is caused by low zinc concentrations in the mother’s breast milk. This type of zinc deficiency is called TNZD because zinc-deficient symptoms only develop during breast-feeding and do not reoccur after weaning. In cases of TNZD, levels of zinc in the milk have been reported to be reduced by 75–90% compared with normal levels (19–21), which probably defines the onset and course of each patient. The low zinc levels in breast milk that result in TNZD are caused by mutations of the ZnT2/SLC30A2 gene in mothers. Symptoms of TNZD are alleviated with zinc supplementation to the infant, but not to the mother. A number of missense mutations and a nonsense mutation of the ZnT2/SLC30A2 gene have been identified. Missense mutations have been shown to cause aggresomal accumulation, lack of zinc transport activity or marked destabilization

Table 1. Zinc transporters whose mutations and SNPs cause inherited diseases.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Diseases</th>
<th>MIM No.</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>ZIP4</td>
<td>Acrodermatitis enteropathica (AE)</td>
<td>201100</td>
<td>Eczematous dermatitis on the perioral, perianal, and acral areas; alopecia; diarrhea; growth retardation and delay; mental slowing; poor wound healing in advanced disease Ameliorated with zinc supplementation (1–3 mg/kg/d)</td>
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<tr>
<td>ZnT2</td>
<td>Transient neonatal zinc deficiency (TNZD)</td>
<td>608118</td>
<td>Erythematous and erosive dermatitis around the mouth, genital region, neck, and fingers; diarrhea; hair loss Ameliorated with zinc supplementation during nursing</td>
</tr>
</tbody>
</table>
in ZnT2 protein (19–21). TNZD likely often occurs in an autosomal dominant inheritance pattern.

In mice, “lethal milk” phenotype (MIM No. 602095), a term derived from the fact that pups nursed by affected dams die before weaning, is known (22). This phenotype is caused by impaired secretion of zinc into the milk and has been shown to be the result of homozygous mutations in the Znt4/Slc39a4 gene (22). However, there have been no reports of a similar condition in humans.

**Remarks**

Zinc is essential for the growth and development of infants and children. Thus, developing possible nutritional strategies to overcome zinc deficiency, in addition to zinc supplementation, would be beneficial to the health of infants and children globally. Moreover, clarification of the molecular mechanisms of AE and TNZD may give important clues to preventing premature and full-term normal infants from developing zinc deficiency, given that some countries may have an increased risk for TNZD (4). In some patients diagnosed with AE, no mutations are found in the ZIP4/SLC39A4 gene, which may suggest that zinc transporters other than ZIP4 may be involved in the zinc absorption process in the small intestine.

**REFERENCES**


