Trace Element Deficiency in Infants and Children
—Clinical practice—

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Abstract: Trace element deficiencies commonly encountered in Japanese infants and children are discussed. Premature birth infants have a high likelihood of developing deficiency of trace elements such as iron, zinc, and selenium, during the period of rapid growth from 2 months to 6 months of age. Breast-fed infants, in particular, are prone to develop trace element deficiency, and alopecia and dermatitis attributable to zinc deficiency have been reported. Furthermore, "follow-up milk" formulas (milk-substitute nutritional supplement for infants) in Japan contain practically no zinc or copper. Dependence on follow-up milk formulas as the main source of nutrition is associated with a high risk of zinc and copper deficiency. In one study, 60% of short-statured children without any endocrine disease were found to have zinc deficiency, and zinc administration was associated with an increase of body height. About 20 to 30% of adolescent and young women exhibit iron and zinc deficiency due to dieting. Excessive iodine intake by mothers during pregnancy has been suggested to be the cause of hyper-TSH-emia detected during the mass screening of neonates. Many enteral formulas in Japan do not contain selenium and iodine, and long-term administration of such formulas has been reported to be associated with deficiency of these elements.

Key words: Premature birth infants; Short-statured children; Infantile iron deficiency; Infantile zinc deficiency

Introduction

Deficiency of trace nutrients is more likely to be encountered in children and pregnant women, who have a larger demand per unit body weight. On a global level, the trace element deficiency status in the population is particularly serious in Southeast Asia and Africa, and 41 to 99% of children in these regions have been reported to be suffering from deficiency of vitamin A, iodine, iron, or zinc.[1)] In Japan, trace element deficiency is seldom encountered

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Table 1 Symptoms, Diagnosis, and Treatment of Major Iron Deficiency in Infants

	Major symptoms	Diagnostic criteria	Treatment
Premature birth infants Late anemia (16 months or later after birth)	Facial pallor, inanimate, dysphoria, anorexia, poor weight gain	Hb≦10 g/d*l*	Iron supplementation (2 mg/kg/day) continued until normalization of the serum iron and ferritin levels 3–4 mg/kg/day if the birth weight is 1,000 g or less Guidance on weaning, follow-up examination (one year after completion of treatment)
Delayed weaning, between 6 months to 2 years after birth (Milk anemia)	Facial pallor, inanimate, dysphoria, anorexia, poor weight gain	Hb≦11 g/d*l*	A. 10 g/d*l*＜Hb≦11 g/d*l*: Guidance on diet, follow-up examination (once a month, every 6 months) B. Hb≦10 g/d*l*: Iron supplementation (3–6 mg/kg/day, 12–14 weeks) Guidance on diet, follow-up for one year after completion of treatment
Adolescent women	Indefinite complaints (malaise, fatigability, palpitation, shortness of breath), facial pallor, decreased attentiveness, asthenia	Hb≦12 g/d*l*	A. 11 g/d*l*＜Hb≦12 g/d*l*: Guidance on diet, follow-up examination (once a month, every 6 months) B. Hb≦11 g/d*l*: Iron supplementation (iron 4–6 mg/kg/day, 12–14 weeks) Guidance on diet, follow-up for one year after completion of treatment
Athletes (Sports anemia)	Same as in adolescent anemia, failure to achieve better records, inability to muster the last spurt	Hb≦12 g/d*l*	Same as for adolescent anemia, decrease in the exercise level

Note 1) Administer ferric pyrophosphate (Incremin syrup®) to infants and small children, and ferrous sulfate (Ferro-Gradumet®), ferrous fumarate (Ferrum®) or ferrous citrate (Ferromia®) to older children.
(Quoted and modified from Yokoyama, M.: *The Journal of Pediatric Practice* 1999; 10: 1437–1444)

in healthy infants and children. However, it poses a problem in premature birth infants and children with poor nutritional intake, patients receiving enteral formulas for prolonged periods, and patients with various chronic diseases.

In this article, we discuss trace element deficiency of the type most commonly encountered in Japanese infants and children. "Trace elements," in general, do not include iron. However, since iron is a trace element and iron deficiency is a particularly important problem in children, iron deficiency is also discussed here.

Iron Deficiency Anemia

1. Diagnosis and treatment of iron deficiency

Iron deficiency anemia occurs more commonly in premature infants (premature birth infants), infants between 6 months and 2 years of age, and adolescent women. In these age groups, the iron demand is particularly high due to the rapid growth of body height. Table 1 shows the symptoms of iron deficiency anemia in children, the diagnostic criteria, and the treatment strategies.[2,3] When a decrease in the hemoglobin level is noted, iron deficiency can be confirmed on the basis of a decreased serum iron level, increased serum total iron-binding capacity, decreased serum ferritin level, and decreased mean corpuscular volume (MCV).

2. Premature infants

The amount of iron delivered from the maternal body to the fetus via the placenta increases during the late gestation period, therefore, iron deficiency is more likely to be encountered in premature infants. Anemia in premature birth infants can be divided into

Table 2 Symptoms of Infantile Zinc Deficiency and Predisposition

Symptoms of deficiency	Factors related to the onset of zinc deficiency
• Symptoms of acute deficiency Eruptions around the mouth, on the pubis, and extremities, skin erosion, alopecia, susceptibility to infections, poor weight gain • Symptoms of chronic deficiency Stagnation of growth of body height, anemia, dysgeusia, susceptibility to infections	Between 2 months and 6 months of age in premature birth infants (especially breast-fed infants), unbalanced diets, short stature, young women, long-term administration of large amounts of iron, chronic diarrhea, diabetes mellitus, nephrotic syndrome, cirrhosis, Crohn's disease, Down's syndrome

early anemia developing around 8 weeks after birth, and late anemia developing 16 weeks or later after birth. Since early anemia is attributable to a decline in hemopoiesis in neonates, iron supplements are not effective, while blood transfusion and erythropoietin injection are effective. The late anemia represents iron deficiency anemia due to depletion of iron stores. Its incidence is high among breast-fed infants and iron supplements are effective in the treatment of this condition.

3. Milk anemia

Anemia occurring between late infancy and early childhood in children with delayed weaning who drink a lot of milk is well known as milk anemia. This has been attributed to insufficient iron intake. It may be associated with protein-losing enteropathy and gastrointestinal bleeding.

4. Adolescent women

Anemia in adolescent women is caused by iron loss due to menstruation, unbalanced diets, and dieting for weight loss. It occurs at a high incidence, and about 8 to 10% of adolescent women are reported to have iron deficiency anemia. When taking iron deficiency without anemia also into account, one out of about four adolescent patients with indefinite complaints is thought to have iron deficiency.[2,3]

5. Athletes

Iron deficiency anemia in athletes is considered to be caused by insufficient iron intake, iron loss, intestinal bleeding, and erythroclasis. This type of anemia is particularly important to be borne in mind when adolescent women, who are already susceptible to anemia, engage in intensive sports activities.[4,5]

Zinc Deficiency (Table 2)

1. Diagnosis and treatment of zinc deficiency

Zinc deficiency in children is characterized mainly by dermatitis and alopecia during infancy, and by short stature during childhood. Zinc deficiency in children is not rare in Japan. Evaluation of age-related variations of serum zinc levels shows that the levels are low because of physiological factors between 2 months to 6 months after birth.[6,7] However, there are as yet no diagnostic criteria specifically established for zinc deficiency in children. Perhaps the same criteria as for adults are applicable (serum zinc level under 65μg/dl).

For the treatment of zinc deficiency, zinc sulfate is administered at the dose of 5 mg/kg/day (1 mg/kg/day of zinc) b.i.d or t.i.d after meals. However, zinc sulfate is not yet approved for use as a drug. Polaprezinc (Promac®) is a zinc-containing preparation that can be taken orally, however, only treatment of gastric ulcer with this drug is covered by the National Health Insurance in Japan.

2. Premature infants

Infants born prematurely and/or breast-fed are particularly prone to develop zinc deficiency between 2 months to 6 months after

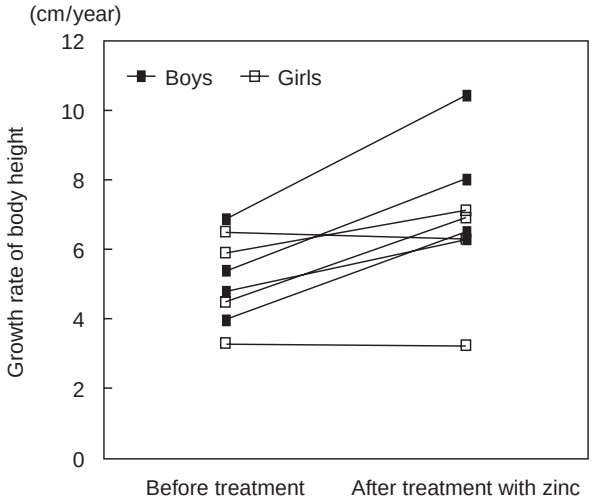

Fig 1 Changes in the growth rate after administration of zinc in children of short stature
(Quoted and modified from Kaji, M. *et al.*: *J American College Nutrition* 1998; 17: 388)

birth.[6,7] Since premature infants have only small stores of trace nutrients in the body, they tend to develop trace element deficiency during the period of rapid growth when the demand for these elements increases. Moreover, since the zinc concentration in breast milk is lower than that in milk formulas, breast-fed infants are more likely to develop zinc deficiency.

Fortified human milk products are available commercially for premature infants fed on breast milk. The appearance of symptoms of acute zinc deficiency, such as alopecia and dermatitis, has been reported even in infants receiving fortified human milk products between 2 months and 6 months of age, when marked increase in the body weight is observed;[8] this is because even though fortified human milk products contain zinc, they are not present in sufficient amounts to satisfy the requirements associated with the rapid increase of body weight.

3. Infants depending on "Follow-up milk" formulas as the main source of nutrition

"Follow-up milk" formulas (milk-substitute nutritional supplement for infants), which are used from 9 months after birth, contain practically no zinc or copper. Although there have been no reports yet, dependence on follow-up milk formulas as the main source of nutrition can lead to zinc and/or copper deficiency.

4. Short-statured children

Out of 30 short-statured Japanese children who did not have any endocrine disease, 18 (60%) had latent zinc deficiency and 11 (37%) showed serum zinc levels below the standard level (under 70μg/dl). Zinc administration is associated with an increase of body height in many cases. The increase is particularly marked in boys receiving zinc supplementation; (Fig. 1).[9] Children with short stature due to zinc deficiency usually do not exhibit other symptoms of zinc deficiency, such as alopecia and dermatitis.

Therefore, when children of short stature are investigated as to the cause, examination for zinc deficiency is essential, and zinc administration may be attempted to improve the height of the children.

5. Young women

About a half of female college students are reported to show serum zinc levels below the standard, and extremely poor nutritional intake of zinc due to dieting and intake of unbalanced diets has been suggested to be the cause.

6. Other patient groups susceptible to zinc deficiency

Children with Down's syndrome, serious psychosomatic disorders, diabetes mellitus, or nephrotic syndrome have a relatively higher likelihood of developing zinc deficiency. Acrodermatitis enteropathica is a congenital zinc absorption disorder, and symptoms of zinc deficiency are typically observed during infancy.

Copper Deficiency

Copper deficiency, like zinc deficiency, is also more likely to develop in premature infants,

but it usually does not cause any clinical problems and copper supplementation is unnecessary. Menkes disease is a congenital abnormality of copper metabolism characterized by severe copper deficiency, but the incidence of this condition is extremely low, and it is rarely encountered in ordinary pediatric practice.

Selenium Deficiency

Selenium deficiency, like iron and zinc deficiency, is also more likely to occur in premature birth infants between 2 months to 6 months of age when they show rapid growth, but it is not associated with any clinical abnormalities. Children taking enteral formulas with little selenium content exhibit marked selenium deficiency. Also, children with conditions such as serious psychosomatic disorders who have lower daily caloric intake than the caloric requirement for age are more prone to develop deficiency of selenium and other trace elements.

Iodine Deficiency

Since Japanese people consume marine products in relatively large quantities, iodine excess may be more of a problem than iodine deficiency. However, some enteral formulas have extremely low iodine content (Ensure Liquid®, Twinline®, Racol®, etc.). Dependence on such enteral formulas as the only source of nutrition is associated with the risk of iodine deficiency.[10] Iodine deficiency may cause goiter and/or hypothyroidism.

Conclusion

This article discusses trace element deficiencies that are relatively commonly encountered in Japanese infants and children. Particularly in the following cases, aggressive examination and treatment are necessary (see the respective sections for treatment).

1) Premature birth infants have a greater likelihood of developing deficiency of trace elements such as iron, zinc, and selenium during the period of rapid growth between 2 months and 6 months of age. Breast-fed infants are particularly susceptible to trace element deficiency.
2) The incidence of latent zinc deficiency is high among children of short stature without endocrine disease, and zinc administration is often associated with an increase in the body height.
3) Deficiency of iron and zinc is often noted in adolescent and young women.
4) Prolonged use of enteral formulas in children is associated with the risk of trace element deficiency, such as selenium and iodine deficiency. Children with serious psychosomatic disorders are particularly likely candidates to develop trace element deficiency. One of the countermeasures is to avoid usage of the same type of enteral formula over prolonged periods of time.

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