Biotin and carnitine deficiency due to hypoallergenic formula nutrition in infants with milk allergy

Brief report

Title : Biotin and carnitine deficiency in infants with milk allergy due to hypoallergic formula nutrition.

Running title: Biotin and carnitine deficiency due to hypoallergenic formula

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Abstract

Amino acid formulas and hydrolyzed formulas given to infants in Japan with milk allergies theoretically contain little, if any, biotin and carnitine. We assessed biotin and carnitine insufficiency in six infants with milk allergies who were fed amino acid formulas and/or hydrolyzed formulas by measuring urine 3-hydroxyisovaleric acid (3-HIA) and serum free carnitine (C0), respectively. All patients presented with an elevated urine 3-HIA level and a lowered serum C0 level compared with post-menstrual age-matched infants who were feed breast milk or standard infant formulas. Supplementation with biotin and L-carnitine immediately improved the insufficiency. Care should be taken to avoid biotin and carnitine deficiencies in allergic infants fed amino acid or hydrolyzed formulas.

Key words

milk allergy, amino acid formula, hydrolyzed formula, biotin deficiency, carnitine deficiency

Introduction

Carnitine is an important cofactor for β-oxidation and in the form of acylcarnitine facilitates the transport of long-chain fatty acids into the mitochondrial matrix[1]. Carnitine could be considered a conditionally essential nutrient in the neonatal population due to the reduced ability of neonates to synthesize carnitine[2]. Biotin is a vitamin that serves as a covalently bound coenzyme for carboxylases, which catalyze essential steps in gluconeogenesis, fatty acid synthesis, and metabolism of odd-chain fatty acids and some amino acids. Concerns have arisen that some types of milk and enteral nutrition formulas used by patients with cow's milk allergies lacked sufficient biotin and carnitine and that use of these products can lead to nutrient deficiency[1].

We recently demonstrated that serum carnitine profiles and urine 3-hydroxyisovaleric acid (3-HIA) are useful markers for detection of biotin deficiency in preterm infants[3]. Moreover, we found that serum free carnitine (C0) levels in preterm infants were significantly lower than those in term infants. Chronic biotin insufficiency frequently occurs in preterm infants, even those fed with maternal milk or standard infant formulas. In this context, preterm infants with milk allergies are at heightened risk for development of biotin and carnitine deficiency after starting hypoallergic formula nutrition. Herein we report on six infants with milk allergies who developed both

biotin and carnitine deficiencies during treatment with amino acid formulas and/or hydrolyzed formulas.

Methods

Six infants born at the University of Fukui Hospital and Toho University Sakura Hospital between July 2010 and March 2012, and diagnosed as having a cow's milk allergy were enrolled (Table 1). The diagnosis of cow's milk allergy was reached when the following criteria were satisfied: 1) no other causes of gastrointestinal symptoms, and 2) the disappearance of gastrointestinal symptoms after changing from a standard cow's milk formula to either amino acid or hydrolyzed milk formula and the recurrence of the symptoms after the re-administration of standard formula. Lymphocyte stimulation tests using cow's milk protein were performed in Case 1, Case 2, and Case 3, revealed a positive result.

3-Hydroxyisovaleric acid was measured by gas-chromatography-mass spectrometry with urease-treated urine, and serum C0 by tandem mass spectrometry without derivatization, according to previously reported methods[4, 5]. Since serum C0 levels in preterm infants are dependent on post-menstrual age, serum C0 levels of post-menstrual age matched control infants who received enteral feeding with maternal milk and/or standard formula made in Japan were used as reference values[3].

Biotin deficiency reduces biotin-dependent enzyme methylcrotonyl-CoA carboxylase activity, resulting in increased urinary excretion of 3-HIA[6]. Elevated levels of urinary 3-HIA outside the normal range (3.4 - 12.5 μg/mg creatinine) are considered a marker

of biotin deficiency.

The study was approved by the Institutional Ethics Committee at the University of Fukui. The parents of the infants gave written consent.

Results

Median gestational age and median birth weight were 199 days (range 173 -250 days) and 1089 g (range 880-2,327 g) (Table 1). All six patients showed elevated levels of urine 3-HIA on day 115 (median), after commencement of amino acid or hydrolyzed milk formula feeding (Figure 1).

Serum C0 levels are generally increased with post-menstrual age in preterm infants fed breast milk or standard infant formulas[3]. However, three patients did not show any significant increase in serum C0 levels during hypoallergic formula feeding (Figure 2). After 68 days (median), range 37-123 days, of treatment with hypoallergenic formula, all patients showed serum C0 levels lower than 20 nmol/ml or the reference level for post-menstrual age matched control infants.

Symptoms of carnitine deficiency such as rhabdomyolysis, hypoglycemia, and convulsion, were not observed in any of the patients. Although Case 3 and Case 6 showed mild elevation of serum creatine kinase, each patient's muscle tonus was normal. Case 2 exhibited well-circumscribed erosive erythema in the anogenital and circumorbital regions and hair loss. Case 5 presented with erosive erythema on the face, and Case 6 developed alopecia with hypopigmented hair. Five patients, all except Case 1, were given oral supplementation with both biotin (0.5-5 mg/day) and L-carnitine

(15-99 mg/kg/day). In Case 1, the patient outgrew the milk allergy, so standard infant formula was started at 392 days of post-menstrual age without any supplementation. The skin lesions in Case 2, Case 5 and Case 6 immediately disappeared after commencement of supplementation and did not recur.

Discussion

There are several reports exclusively in Japan of biotin deficiency occurring in infants fed amino acid or hydrolyzed formula due to milk allergy[1,7]. The observation that biotin deficiency due to hypoallergic infant formula nutrition is rare in other countries may be due to the fact that supplementation of hypoallergic formulas with biotin as a food additive is not permitted in Japan. We recently demonstrated that there is a risk of biotin deficiency even in preterm infants fed maternal milk or standard infant formulas[3]. In the present study, although none of the infants exhibited severe symptoms of biotin deficiency such as seizures, hypotonia, lactic acidosis, and organic aciduria, half of them presented with skin lesions. The anogenital erosive erythema and hypopigmented hairs might be caused by zinc and copper deficiency, respectively. However they disappeared after commencement of biotin but not zinc or copper supplementation, suggesting that biotin deficiency is common in preterm infants fed hypoallergic formulas.

In contrast to the skin lesions characteristic of biotin deficiency, carnitine deficiency is difficult to recognize in the infantile period, because its early symptoms are failure to thrive and impaired function of organs such as cardiac muscle and skeletal muscle that are highly dependent on fatty acid oxidation for fuel[8]. Once vital energy is exhausted upon fasting or starvation, defective β-oxidation of fatty acids due to carnitine

deficiency may produce pathological situations such as sudden infant death syndrome, Reye-like episodes, hypoketotic hypoglycemic coma, muscle weakness, and profound cardiac dysfunction. Since the patients developed carnitine insufficiency coincident with or prior to biotin deficiency, physicians should be aware of the possible comorbidity of carnitine deficiency in milk-allergic infants treated with hypoallergic formulas when typical skin lesions associated with biotin deficiency develop.

It has been shown that parenteral nutrition without carnitine supplementation in both term and premature infants resulted in decreased carnitine plasma concentrations, and that carnitine supplementation in paraenteral nutrition enhanced fatty acid oxidation and clearance, improved lipid tolerance, and increased nitrogen balance in the neonates[2]. These findings suggest that carnitine supplementation might allow for more rapid growth and better fat utilization in infants fed amino acid or hydrolyzed formulas.

Weaknesses of the current study include the small sample size and methodologic limitations, specifically with respect to assessment of metabolic and anthropometric measurements, and the dosing regimens for carnitine supplementation. For ethical reasons, the patients were treated with different doses of carnitine with the goal of maintaining serum C0 concentration over 20 nmol/ml, which is the reference value for diagnosis of carnitine deficiency[1, 9]. Future studies evaluating the effects of carnitine

and biotin supplementation on infantile morbidity parameters should include an assessment of different dosing regimens.

In conclusion, when treating milk-allergic infants with amino acid or hydrolyzed formulas, supplementation of biotin and carnitine is recommended. It would be beneficial if hydrolyzed and amino acid formulas produced in Japan could be fortified with biotin and carnitine.

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Figure legends

Figure 1　Urinary excretion of 3-hydroxyisovaleric acid (3-HIA) increased in infants fed amino acid formula and/or hydrolyzed formula. Each patient's urinary excretion of 3-HIA before (open symbols) and after (closed symbols) commencement of hypoallergic formula nutrition is indicated as the urinary concentration of 3-HIA adjusted for urinary concentration of creatinine. Broken lines represent the period of biotin supplementation. The shaded rectangle denotes the normal range of 3.4-12.5 μg/mg Cre reported by Mock *et al.* [5].

Figure 2　Serum free carnitine (C0) decreased in infants fed with amino acid and/or hydrolyzed formula. Each patient's serum C0 concentration before (open symbols) and after (closed symbols) commencement of hypoallergic formula nutrition is indicated. Broken lines represent the period of carnitine supplementation. Reference values (x) for post-menstrual age-matched control infants who were fed maternal milk or standard infant formula made in Japan are indicated[3]. The solid line and the shaded polygon delineate the mean of reference values and 95% limit of agreement.