



Patient Report

Severe hypoglycemic encephalopathy due to hypoallergenic formula in an infant

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Abstract A 7-month-old girl was brought to hospital due to vomiting. Upon admission, she was in a convulsive state and stupor with extremely low blood glucose. Head computed tomography showed brain edema, and comprehensive treatment for acute encephalopathy was initiated immediately. Severe hypoglycemia, metabolic acidosis, elevation of ammonia and serum transaminases and creatine kinase suggested metabolic decompensation. Infusion of a high-glucose solution containing vitamins, biotin, and L-carnitine resolved the metabolic crisis quickly, but brain damage was irreversible. She was found to have been fed exclusively on a hypoallergenic formula (HF) for 7 months, although she was found later to be non-allergic. Evidence of inborn metabolic diseases was absent, therefore biotin deficiency and carnitine deficiency were concluded to be a consequence of reliance on a HF for a prolonged period. Health-care professionals should warn parents of the consequences of using HF.

Key words acute encephalopathy, biotin deficiency, carnitine deficiency, hypoallergenic formula, hypoglycemia.

Most hypoallergenic formulas (HF) available in Japan are not fortified with biotin or carnitine.¹ Severe metabolic decompensation can be induced by biotin deficiency (BD) or carnitine deficiency (CD) in prolonged starvation, and supplementation of these nutrients has been recommended when treating milk-allergic infants with amino acids or hydrolyzed formulas alone.² HF, however, are available without prescription, making it possible for parents of milk-allergic infants or infants without allergies to obtain HF at their discretion.

We report a severe case of hypoglycemia induced by HF-derived BD and CD that resulted in acute encephalopathy and irreversible brain damage in an infant who was not allergic to cow's milk. This case emphasizes the need for pediatricians and health-care professionals to educate parents about food allergies and warn them about this preventable metabolic crisis.

Case report

A 7-month-old girl was transferred to hospital with a 2 day history of vomiting and poor feeding. Diarrhea was not remarkable. She was observed at home without medical intervention for over 30 h. Upon hospital admission, she was in a convulsive state and stupor (Glasgow coma scale score 8, E2, V2, M4), with tachycardia

and low blood pressure. Bodyweight had decreased by 5%, and capillary refilling time was elongated. Blood glucose was 8 mg/dL.

Bolus infusion of 20% glucose was given followed by rapid infusion of extracellular fluids. Head computed tomography showed diffuse edema (Fig. 1). Methylprednisolone pulse therapy, immunoglobulin, edaravone, and mannitol were started immediately to treat acute encephalopathy. Diffusion-weighted magnetic resonance imaging (MRI) showed increased signal intensities in the cortical and subcortical white matter in the occipital lobe over both cerebral hemispheres (Fig. 2). Erythema and hair loss were absent. Influenza virus and Respiratory syncytial virus antigens were negative, but norovirus antigen was detected in stools 2 days later. Extreme hypoglycemia, severe acidemia, and elevation in ammonia and serum transaminases and creatine kinase suggested severe metabolic decompensation (Table 1). Although the primary metabolic cause was yet to be identified, a high-glucose, protein-free infusion was started with vitamins, biotin, and L-carnitine. On tandem mass spectrometry of dried blood spots, free carnitine was low and 3-hydroxyisovalerylcarnitine was elevated. Urinary organic acid analysis indicated elevated lactate, 3-hydroxypropionic acid, 3-hydroxyisovaleric acid, and 3-methylcrotonylglycine. Metabolic status and liver dysfunction recovered rapidly, but brain edema progressed. On day 7 of admission, brainstem auditory-evoked potentials on both sides disappeared. Electroencephalography on day 14 showed no brain activity. She had no sign of spontaneous movement and respiration despite treatment, and progressed to brain death.

Subsequently, serum biotin concentration, measured as previously described,³ was confirmed to be low. Her record of newborn screening was collected to ascertain if her deficiency was

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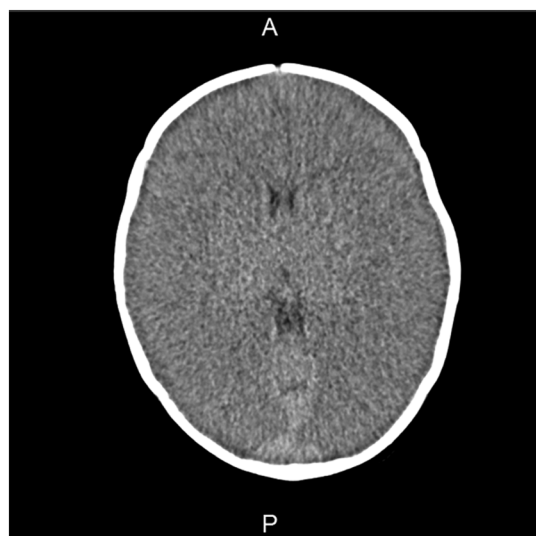


Fig. 1 Brain computed tomography showing diffuse brain edema.

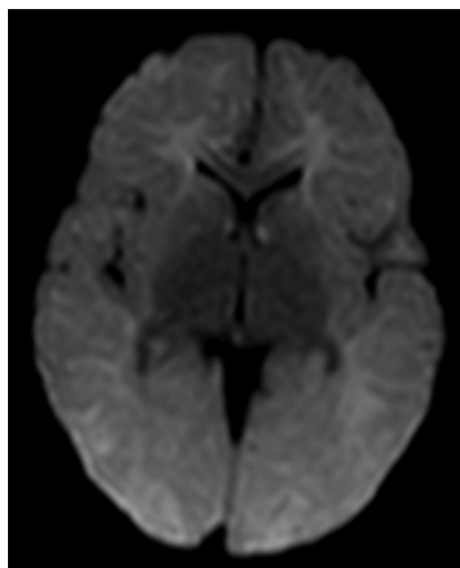


Fig. 2 Diffusion-weighted brain magnetic resonance imaging showing increased signal intensity in the cortical and subcortical white matter in the occipital lobe over both cerebral hemispheres.

congenital; no CD or elevation of 3-hydroxyisovaleryl carnitine was observed. Biotinidase activity was intact. Carnitine clearance was not increased.

She was found to have been fed exclusively on an HF from 2 weeks of age, and solid food had just been introduced. She had not been treated with pivalic acid-containing antibiotics or anti-epileptic agents. We concluded that BD and CD were caused by prolonged nutrition with an HF.

Her elder brother had a history of anaphylaxis triggered by cow's milk, and dairy products had been restricted during infancy. Her second brother was given an HF and breast milk, but did not manifest symptoms of milk allergy. Neither had a metabolic crisis. The patient had never been diagnosed as being allergic to cow's milk, but her mother chose to feed her with an HF. Introduction of solid food had been delayed for fear of developing food allergy.

After stabilization of her condition, specific serum IgE dose test and skin prick test were conducted; both were negative for reaction to cow's milk. A standard formula was started via enteral feeding, and no allergic reaction (e.g. erythema) was observed.

Discussion

Biotin is a cofactor of four important carboxylases, each of which plays a key role in fatty acid synthesis, gluconeogenesis, or metabolism of several amino acids. BD leads to deficiency of these biotin-dependent carboxylases, which provokes life-threatening metabolic derangements. Inborn BD is caused by biotinidase deficiency. Acquired BD is rare, but cases of BD have been reported in infants fed with HF because biotin was not allowed to be added to HF until recently in Japan.⁴ BD often manifests as skin lesions, alopecia or neurologic symptoms before metabolic derangements.

Carnitine carries long-chain fatty acids across mitochondrial membranes to the matrix, where they are used in beta-oxidation. When carnitine is low, beta-oxidation of these fatty acids is restricted, resulting in energy depletion and hypoglycemia in prolonged starvation. Primary CD is a genetic disorder of carnitine transporters. Organic acidurias and other metabolic disorders can cause secondary CD. It can also be iatrogenic, as seen in patients treated with pivalic acid-containing antibiotics⁵ or anti-epileptic agents.⁶ In Japan, carnitine is not supplemented in special formulas, and infants fully reliant on them are at risk of developing CD. Unlike BD, detection of CD before serious hypoglycemia is difficult.

The present patient did not have skin lesions or neurologic symptoms suggestive of BD before the event. Skin lesions in BD are caused by deficiency of acetyl-CoA carboxylase. The present BD may not have been sufficiently severe to cause serious metabolic derangements under normal circumstances.

Hypoglycemia in CD is acknowledged as non-ketotic due to inhibition of beta-oxidation of long-chain fatty acids. In the present patient, however, severe hypoglycemia was accompanied by elevation of ketone bodies. In primary CD, low free carnitine in serum reflects deficiency of carnitine in tissue, which results in inhibition of beta-oxidation. In cases of low carnitine intake, however, urinary loss is minimized, and tissue carnitine level may not be as low as the serum free carnitine level suggests.⁷ This mechanism of elevation of ketone bodies may have occurred in the present case. With a lower-than-ideal carnitine level, however, beta-oxidation and ketogenesis could not prevent severe hypoglycemia.

The present patient also had low biotin. In energy deprivation, acetyl-CoA produced by beta-oxidation stimulates pyruvate carboxylase (PC) to induce gluconeogenesis, which provides essential glucose to important organs (especially the brain). In BD, however, PC is impaired, and pyruvate cannot be metabolized further for gluconeogenesis. In the present patient, the 3-hydroxybutyrate/acetoacetate ratio was low while the lactate/pyruvate ratio was high, suggesting PC impairment. Concomitant deprivation of biotin and carnitine explains the severe hypoglycemia in the present patient. Delay in pursuing medical attention may have contributed to the severity of hypoglycemia. High lactate/pyruvate ratio may be attributed also to transient mitochondrial dysfunction induced by prolonged hypoglycemia and acidosis.

Table 1 Laboratory data on hospital admission

Biochemistry				Venous blood gas analysis	
T-bil	0.19 mg/dL	NH ₃	194 µg/dL	pH	7.128
TP	6.9 g/dL	PG	8 mg/dL	pCO ₂	33.3 mmHg
Alb	4.8 g/dL	Total ketone	10 430 µmol/L	HCO ₃ ⁻	10.8 mmol/L
AST	211 IU/L	AcAc	4978 µmol/L	BE	-17.3 mmol/L
ALT	129 IU/L	3-OHB	5453 µmol/L	AG	32.2 mEq/L
LDH	1188 IU/L	NEFA	2830 µEq/L	Tandem mass spectrometry	
ALP	580 IU/L	Lactate	41.4 mg/dL		
CK	2350 IU/L	Pyruvate	1.62 mg/dL		
BUN	42.9 mg/dL	Blood count		C0	4.07 nmol/mL
Cre	0.39 mg/dL			(Cut off:	<8 nmol/mL)
UA	25.3 mg/dL	WBC	4300 /µL	C5-OH	1.66 nmol/mL
Na	149 mEq/L	RBC	463 × 10 ⁶ /µL	(Cut-off	1 nmol/mL)
K	6.2 mEq/L	Hb	12.1 g/dL	Others	
Cl	106 mEq/L	Plt	56 × 10 ⁴ /µL		
Ca	9.3 mg/dL				
P	7.6 mg/dL				
CRP	1.53 mg/dL			Serum biotin	2.4 ng/dL
				(normal range	4.7–22.0 ng/dL)
				Free carnitine clearance	0.6%
				(normal range	<2.0 %)

3-OHB, 3 hydroxybutyrate; AcAc, acetoacetate; AG, anion gap; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; C0, free carnitine; C5-OH: 3-hydroxyisovalerylcarnitine; CK, creatine kinase; Cre, creatinine; CRP, C-reactive protein; Hb, hemoglobin; LDH, lactate dehydrogenase; NEFA, non-esterified fatty acid; PG, plasma glucose; Plt, platelets; RBC, red blood cells; T-bil, total bilirubin; TP, total protein; UA, uric acid; WBC, white blood cells.

Given that viral isolation of cerebrospinal fluid was not carried out, the possibility of norovirus encephalopathy cannot be denied, but MRI showed increased intensity in diffusion-weighted imaging in the cerebral cortex and deep white matter, compatible with hypoglycemic encephalopathy.⁸ In the present patient, follow-up MRI was not done due to deterioration in her condition, therefore it is unknown whether MRI showed the typical changes of hypoglycemic encephalopathy.

The issue of BD and CD due to HF has attracted the attention of many pediatricians, especially since the Japan Pediatric Society issued an alert in 2012. Although a similar case has been reported, the present case is noteworthy in two aspects: (i) BD and CD can result in hypoglycemic encephalopathy that may lead to irreversible brain damage under certain circumstances; and (ii) it illustrates that HF are not always used under professional supervision. Anxiety about food allergy is widespread among parents, and HF can be obtained without prescription. In the present case, a diagnosis of milk allergy was not made by health-care professionals, and the HF was started at the mother's discretion. She was not aware of the possible consequences of BD and CD, and a physician was not involved. Some HF are now supplemented with biotin and carnitine, but not all. The present case calls for pediatricians and health-care professionals to educate parents about food allergies and to warn them of the consequences of relying exclusively on non-supplemented formulas.

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Disclosure

The authors declare no conflicts of interest.

Author contributions

E.O, Y.T, and M.I. gave medical care; E.O. and M.I. drafted the manuscript; H.K. measured biotin concentration; T.F. designed the manuscript outline and gave conceptual advice; S.T. supervised the whole study process. All authors read and approved the final manuscript.

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