

Infantile hepatic dysfunction improved by elimination of cows' milk formulas

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We present three infants who showed hypertransaminasemia without extrahepatic symptoms, which improved by eliminating cows' milk formulas. The levels of milk protein-specific lymphocyte proliferation were elevated in all three patients. These cases indicate the importance of food allergy in the diagnosis of infantile hepatic dysfunction.

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The elevation of serum aminotransferase without severe liver dysfunction such as cholestasis or coagulopathy is not a rare condition in infancy. The differential diagnosis of this condition should include hepatocellular inflammation (hepatitis), drug- or toxin-associated liver injury, hypoperfusion or hypoxia, passive congestion and non-hepatic disorders (1). Repetitive, sometimes invasive, examinations are usually required to make a diagnosis.

The serum aminotransferase levels were significantly elevated in infants with atopic dermatitis (2). We also noticed infants who developed milk-induced gastroenteropathy complicated with hepatic dysfunction (3). These findings indicate that food allergy can induce hepatic dysfunction. However, allergy-associated liver dysfunction without extrahepatic symptoms such as eczema or diarrhea has not yet been reported.

In this paper, we present the case reports of three infants who showed isolated hypertransaminasemia without any other allergic symptoms. Hepatic dysfunction in these infants was improved by just eliminating cows' milk formulas (CMF) from their diet. These cases indicate the importance of food allergy in the diagnosis of infantile hepatic dysfunction.

Case reports

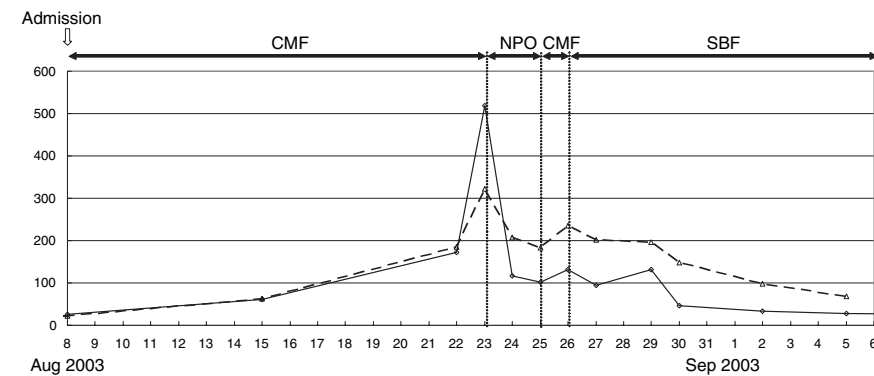
Case 1

A 6-month-old Japanese girl developed hypertransaminasemia. She had been hospitalized since birth for cerebral palsy, delayed psychomotor development, and epilepsy caused by severe neonatal distress. She had received phenobarbital, valproic acid, clobazam, and intramuscular adrenocorticotrophic hormone as antiepileptic agents. She had been bottle-fed. Jaundice, hepatosplenomegaly, diarrhea, or eczema were not recognized when she developed hypertransaminasemia. Serum albumin, total bilirubin, and blood coagulation tests were within normal limits. Hepatitis B surface antigen (HBs-Ag) and anti-hepatitis C antibody3 (HCV-Ab) were both found to be negative (Fig. 1).

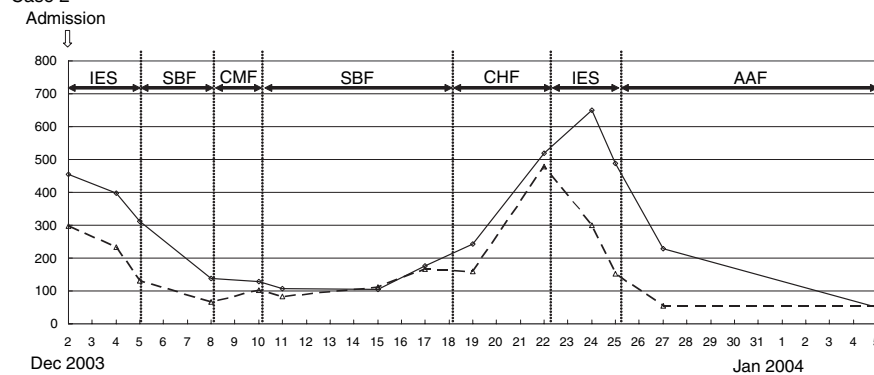
Neither the levels of serum IgE nor the milk-specific IgE were increased (Table 1). Milk protein-specific lymphocyte proliferation was measured by flow cytometry, and the stimulation index was expressed as stimulation index measured by flow cytometry (SIF) (4). The SIF level for β -lactoglobulin was elevated to 189 (normal range < 170).

The CMF and valproic acid were discontinued from August 23, 2003, when the levels of

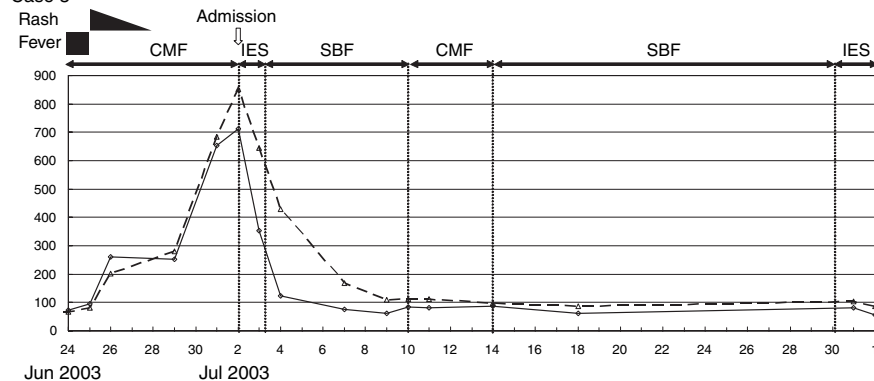
Case 1



Case 2



Case 3



Cows' milk formulas (CMF)

Isotonic electrolytes solution (IES)

Soy-based formula (SBF)

Casein hydrolysate formulas (CHF)

Non per oral (NPO)

Amino acid formula (AAF)

—○— Aspartate aminotransferase (AST) (IU/l)

- - -△- - - Alanine aminotransferase (ALT) (IU/l)

Fig. 1. Clinical courses of three infants. Cows' milk formulas (CMF), isotonic electrolytes solution (IES), soy-based formula (SBF), casein hydrolysate formulas (CHF), non-per oral (NPO), amino acid formula (AAF), —○— aspartate aminotransferase (AST) (IU/l), —△— alanine aminotransferase (ALT) (IU/l).

aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 529 IU/l and 323 IU/l respectively. The infant received par-enteral fluid therapy without enteral feeding for 2 days. Subsequently, AST and ALT rapidly decreased to 101 IU/l and 183 IU/l, respectively, on August 25. An open challenge with CMF was performed from August 25 to 26,

which resulted in elevation of aminotransferase (AST to 131 IU/l and ALT to 236 IU/l). Soy-based formula (SBF; Bonrakuto®, Wakodo, Tokyo, Japan) feeding was started thereafter by discontinuing CMF, and aminotransferase gradually returned to normal. Re-administration of valproic acid did not influence the aminotransferase levels.

Table 1. The tests for allergy in present cases

	Normal range	Case 1	Case 2	Case 3
Total IgE (U/ml)		3	3.59	9.7
Milk-specific IgE (U/ml)		<0.35	0	0.16
SIF				
α -Casein	<330	162	566	875
β -Lactoglobulin	<170	189	172	367
Bovine serum albumin	<150	ND	150	296

SIF, stimulation index measured by flowcytometry; ND, not done.

Case 2

A 6-month-old Japanese boy was referred to us on December 1, 2003 for persistent hypertransaminasemia that was refractory to treatment with various agents such as ursodeoxycholic acid, glutathione, and intravenous immunoglobulin (Fig. 1). When he was 1 month old, he was diagnosed with cytomegalovirus (CMV) hepatitis in another hospital as he showed hypertransaminasemia and elevated levels of IgG and IgM antibodies for CMV. He had been bottle-fed. On admission, jaundice, hepatosplenomegaly, diarrhea, or eczema were not recognized. Laboratory investigations revealed hypertransaminasemia with the levels of AST and ALT being 298 IU/l and 455 IU/l, respectively. Total bilirubin, serum albumin, ammonia, and blood coagulation tests were within normal limits. Blood and urine amino acid were also within the normal range. HCV-Ab and HBs-Ag were found to be negative, while IgG antibodies for CMV and herpes simplex virus were positive. Ultrasonographic examinations of the liver showed normal appearance.

Neither serum IgE nor milk-specific IgE levels were increased (Table 1). The SIF levels for both α -casein and β -lactoglobulin were elevated to 566 (normal range < 330) and 172, respectively.

The CMF was discontinued from December 1. Then, isotonic electrolytes solution and thereafter SBF were used as diet. On December 8, the levels of AST and ALT decreased to 67 IU/l and 138 IU/l, respectively. An open challenge with CMF was conducted from December 8 to 10, which induced an increase in AST level, raising it to 102 IU/l. Although SBF feeding was restarted after discontinuing CMF from December 10, aminotransferase levels gradually increased. Therefore, SBF was discontinued and casein hydrolysate formula was started; however, this resulted in further elevation of aminotransferase levels (AST to 479 IU/l and ALT to 518 IU/l on December 22). Finally, after 2 days of fasting, amino acid formula (Elemental Formula®; Meiji, Tokyo, Japan) was started, and it successfully normalized aminotransferase levels.

Case 3

A 2-month-old, previously healthy Japanese boy was referred to us on July 2, 2003 for elevated aminotransferase after fever and systemic rash from June 24 to June 26, 2003 (Fig. 1). He had been bottle-fed. On admission, jaundice, hepatosplenomegaly, diarrhea, or eczema were not recognized. Laboratory investigations revealed hypertransaminasemia with the levels of AST and ALT being 711 IU/l and 853 IU/l, respectively. Total bilirubin, serum albumin, ammonia, and blood coagulation tests were within normal limits. Blood and urine amino acid were also within the normal range. Serological tests for CMV and Epstein-Barr virus, HCV-Ab, and HBs-Ag were negative. Ultrasonographic examinations of the liver showed normal appearance.

Neither the levels of serum IgE nor the milk-specific IgE were increased (Table 1). SIF levels for α -casein, β -lactoglobulin, and bovine serum albumin were all elevated to 875, 367, and 296 (normal range < 150), respectively.

The CMF was eliminated in the diet from July 2. Then, the infant was fed with isotonic electrolytes solution and thereafter with SBF. As a result the levels of AST and ALT rapidly decreased to 83 IU/l and 111 IU/l, respectively, on July 10. An open challenge with CMF was performed from July 10 to July 14. As AST increased to 86 IU/l on July 14, the test was regarded as positive. Thus, SBF feeding was restarted after discontinuing CMF. About a month later, casein hydrolysate formula (New MA-1®; Morinaga, Tokyo, Japan) was started as a substitute for milk by discontinuing SBF because a slight increase in aminotransferase levels persisted and diarrhea developed. Thereafter, diarrhea disappeared, and aminotransferase levels normalized completely.

Discussion

Cows' milk is one of the most important causes of food allergy during infancy, which is sometimes caused by cell-mediated hypersensitivity (5). The diagnosis of food allergy requires following findings: (i) amelioration of symptoms after elimination of the suspected food antigen, (ii) development of similar clinical reactions after oral challenge, and (iii) demonstration of the sensitization of the patient to the allergen (6).

As the present cases showed isolated hypertransaminasemia that improved after elimination of CMF, they were suspected of having cows'

milk intolerance. The positive results of milk protein-specific lymphocyte proliferation tests indicate that the T cells of these patients had been sensitized to cows' milk proteins, although they showed negative milk-specific radioallergosorbent test. Case 1 showed positive results for food challenge tests and completely met the criteria stated above, which suggests that liver specific delayed type hypersensitivity may exist. On the contrary, in cases 2 and 3, the elevation of aminotransferase during CMF challenge was not satisfactory. Although the reason is actually unknown, short-term challenge might be insufficient to cause liver injury after the cessation of hepatic inflammation. Furthermore, the onset of milk-induced liver injury might require additional factors, such as infection, which alter intestinal permeability and result in an increased uptake of milk antigens. However, they showed the effectiveness of elimination of CMF, and sensitization of lymphocyte to milk proteins, which have not been reported before.

An increase in antigen-specific lymphocyte proliferation reflects clonal expansion of the sensitized T cells, and is considered to be useful in the diagnosis of delayed-type hypersensitivity. As cows' milk protein-specific lymphocyte proliferation was increased in all cases, delayed-type hypersensitivity against cows' milk can be related to their hepatic dysfunction. However, clinical symptoms of food allergy are usually related to organs such as the intestines, skin, or respiratory tract. To our knowledge, this is the first report of isolated hepatic dysfunction caused by food allergy.

The liver is an organ in which bacterial products and food-derived antigens flow from the intestines and interact with the T cells. Therefore, the liver has been considered to play an important role in the induction of T-cell tolerance (7). Previous studies have shown that the Kupffer cells, sinusoidal endothelial cells and hepatocytes themselves present antigenic peptides. Hepatocytes presenting antigens could be targets for the cytotoxic effector function of CD8⁺ cells (8). Furthermore, as activated CD8⁺ T cells express FasL, they could damage hepatocytes by ligation of Fas expressed on the surface of hepatocytes, irrespective of antigen presentation – a mechanism termed as collateral damage (9). These T-cell-mediated hepatocyte injuries may explain the mechanism of hepatic dysfunction associated with cell-mediated hypersensitivity against food, although much remains to be elucidated.

Although cases 2 and 3 also developed hypertransaminasemia or diarrhea after introduction of SBF feeding, these symptoms suggest the coexistence of hypersensitivity to soybean. A rise in the aminotransferase levels in case 2 after casein hydrolysate formula feeding seems to be an allergic response to incompletely hydrolyzed milk proteins (10) because it subsided by the use of amino acid formula.

The present cases may indicate that cell-mediated hypersensitivity to cows' milk is associated with liver injury in infancy. Therefore, it may be of worth to remove CMF from the diet of infants showing isolated elevation of serum aminotransferase. If the hepatic dysfunction improves after the removal, these infants could be saved from many unnecessary examinations, which would be beneficial for them.

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