Hypoglycemic Coma in a Patient with Anorexia Nervosa Coincident with Acute Exacerbation of Liver Injury Induced by Oral Intake of Nutrients

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Abstract

A 33-year-old woman with anorexia nervosa was admitted because of severe malnutrition. Acute liver injury was observed soon after the beginning of oral intake. She was prohibited from eating for 10 days and treated with parenteral nutrition until liver dysfunction was improved. One week after resuming oral intake, she presented severe hypoglycemic coma along with acute exacerbation of hepatocytic injury. Clinical laboratory data suggest that insufficient gluconeogenesis in acute liver injury was involved in severe hypoglycemia. We should be careful of severe hypoglycemia in patients with anorexia nervosa after resuming oral ingestion when signs of liver damage are detected, although hypoglycemic coma is uncommon in anorexia nervosa.

Key words: hypoglycemia, liver injury, anorexia nervosa


Introduction

Anorexia nervosa is associated with many medical complications such as cardiovascular problems, endocrine disorders, electrolyte and hematopoietic abnormalities, amenorrhea and osteoporosis. Refeeding syndrome is also a well-known complication related to nutritional treatment (1). In contrast to those complications, either hypoglycemic coma or severe liver damage is uncommon in patients with anorexia nervosa, although some cases have been reported (2). We report here a 33-year-old woman with anorexia nervosa who experienced hypoglycemic coma coincident with acute exacerbation of liver damage one week after resuming oral intake.

Case Report

A 33-year-old woman visited a nearby hospital because of severe lethargy. Ten years previously, just after she broke up with her male partner, she became anorectic and soon her weight declined from 52 kg to 35 kg. She frequently did self-induced vomiting during the course of weight loss. She experienced wrist and rib fractures due to trauma when she was 18 and 32 years old, respectively. Otherwise her past medical history was unremarkable, except for amenorrhea. She had eaten only one bowlful of rice a day since some weeks before visiting the hospital. According to the DSM-4, since she had body image disturbance, amenorrhea and severe emaciation, she was diagnosed as anorexia nervosa. She was then transferred to our hospital in order to undergo a thorough examination and treatment, because she faced life-threatening emaciation and dehydration. On admission, her height and body weight was 157 cm and 30 kg, respectively, and her body mass index (BMI) was 12.3 kg/m². She was alert and her blood pressure was 102/67 mmHg. She presented bradycardia, 33 bpm, and hypothermia, 34.8°C. Physical examination revealed sign of dehydration, severe emaciation and slight anemia.

Hematological test revealed macrocytic anemia with hemoglobin of 10.2 g/dL, MCV of 112.6 fl and reticulocyte of 1.5%. Blood chemistries were as follows: Total protein 5.1 g/dL, albumin 2.7 g/dL, blood urea nitrogen 16 mg/dL, creatinine 0.5 mg/dL, sodium 139 mEq/L, potassium 4.9 mEq/
Figure 1. Biochemical parameters of blood samples obtained from the subject during hospitalization. On day 40, acute exacerbation of liver damage and hypoglycemic coma was seen. At that time, oral intake of 400 kcal a day and parenteral nutrition of 150 kcal a day was administered to the patient. Parenteral nutrition consisted of 120 kcal of amino acids (shaded area), and the amount of glucose is indicated in the open areas.

L, chloride 102 mEq/L, calcium 7.6 mg/dL, inorganic phosphate 3.4 mg/dL, AST 65 IU/L, ALT 47 IU/L, γGT 191 IU/L, total bilirubin 0.5 mg/dL, C-reactive protein 0.0 mg/dL, creatine kinase 139 IU/L, amylase 96 IU/L, fasting plasma glucose 63 mg/dL. Hormone data revealed high serum growth hormone level, 29.1 ng/mL (reference range <3.0), and low free triiodothyronine level, 1.67 pg/mL (reference range 2.3-4.2), both of which were compatible with anorexia nervosa. Electrocardiogram showed sinus bradycardia, and no abnormalities were found in radiological examinations.

We started a nutritional support to improve her physical condition, that is, oral ingestion of 600 kcal a day and intravenous infusion of 1,000 mL a day containing 150 kcal of glucose and a cocktail of sufficient B vitamins including 20 mg/day thiamine. Serum levels of aminotransferase were gradually increased to AST of 2,569 IU/L and ALT of 2,034 IU/L, and PT-INR as a coagulation indicator was worsened to 1.46 on the 18th hospital day (Fig. 1). Serologic tests for hepatitis A, B, and C viruses were all negative and there was no evidence of alcohol abuse or using hepatotoxic drugs. Ultrasound examination showed signs of fatty liver and a small amount of ascites, and otherwise there were no apparent signs of refeeding syndrome. We did not observe pleural or pericardial effusion or signs of heart failure or edema.

We prohibited her from oral intake, and parenteral nutrition was continued with continuous peripheral intravenous infusion, 500 kcal in 1,500 mL a day, since oral intake of nutrient could be involved in her liver damage. Liver damage was then gradually ameliorated. On the 28th hospital day, laboratory data were improved to AST 482 IU/L, ALT 807 IU/L, plasma glucose 62 mg/dL and PT-INR 1.03 (Fig. 1). During the course of parenteral nutrition, asymptomatic hypoglycemia around 35 mg/dL was sometimes observed. On the 33th hospital day, we resumed oral intake of 250 kcal a day with restriction of fat 5 g a day and gradually increased the amount of calorie. Intravenous infusion was continued to supply rest of calorie and fluid required.

On the 40th hospital day, she became unconscious in the morning. At that time oral intake was 400 kcal a day and the rate of intravenous infusion was 150 kcal a day (Fig. 1). Plasma glucose level was no more than 10 mg/dL, and she regained full consciousness by intravenous administration of glucose. At the same time, the level of serum immunoreactive insulin was <1.0 mU/L, and serum cortisol and growth hormone levels were 68.8 μg/dL and 31.7 ng/mL, respectively. The same sample showed that serum levels of AST, ALT, total bilirubin and PT-INR elevated again to 1,348 IU/L, 1,530 IU/L, 4.0 mg/dL and 1.52, respectively. Once again, we prohibited her from oral intake and changed to totally parenteral nutrition with intravenous infusion through central venous line, starting at 600 kcal a day. She occasionally had asymptomatic hypoglycemia with plasma glucose levels around 40 mg/dL during total parenteral nutrition.

During the course of parenteral nutrition in which the calories were gradually increased, liver damage was improved slowly but steadily. Accordingly, she did not experience further consciousness disturbance due to hypoglycemia, and the level of plasma glucose harbored around 100 mg/dL. We increased the calorie of parenteral nutrition to 1,000 kcal (880 kcal of glucose and 120 kcal of amino acids) and oral feeding was commenced on the 51th hospital day. Four months later, laboratory data were almost normalized.
(Fig. 1), and she never had experience of significant hypoglycemia again.

Plasma glucose levels of the patient were negatively correlated with PT-INR ($r=0.77$, $p<0.05$), AST ($r=0.53$, $p<0.05$) and ALT ($r=0.69$, $p<0.05$), but not with serum bilirubin levels. Plasma glucose levels were not correlated with serum inorganic phosphate that remained at more than 2.6 mg/dL. This observation strongly suggests that liver dysfunction was involved in the low plasma glucose concentrations.

**Discussion**

The presence of severe hypoglycemia in anorexia nervosa patients is clinically important, because it may predict a poor prognosis (4), although moderate hypoglycemia is common and usually asymptomatic among them. The first case that had presented an episode of reversible hypoglycemic coma was reported in 1984 (3). Severe hypoglycemia, with plasma glucose levels as low as 18 mg/dL is rarely observed in patients with anorexia nervosa, but it has been reported in some cases (2-4). The precise pathogenesis of hypoglycemia has not been elucidated, but several mechanisms, including excessive exercise, depletion of liver glycogen, defective gluconeogenesis and failure of glucagon secretion, have been proposed (2).

The present case showed an episode of hypoglycemic coma along with acute exacerbation of liver damage during taking nutrient both orally and intravenously. The causes of liver damage in anorexia nervosa include many different factors, such as starvation itself, rapid refeeding followed by refeeding syndrome and acute hyperperfusion (5-7). Refeeding syndrome usually occurs within four days of starting to feed. Patients can develop fluid and electrolyte disorders, especially hypophosphatemia, along with pulmonary, cardiac and neuromuscular complications as well as liver damage. Most effects result from a sudden shift from fat to carbohydrate metabolism and a sudden increase in insulin levels after refeeding. Recent studies also indicated that lower BMI might significantly contribute to the development of hepato-cellular injuries in anorexia nervosa patients prior to any nutritional treatment (8). In many cases, malnutrition caused liver damage that was recovered rapidly after an appropriate nutritional support (5, 6, 9). In contrast, in the present case oral calorie intake did not improve the liver damage, which rather deteriorated at the early period of the treatment. The fact that she experienced liver damage in spite of nutritional support suggests that refeeding syndrome might be involved in her liver damage. In contrast to this hypothesis, liver damage seemed to improve after stopping oral ingestion, even though we increased the calorie of parenteral nutrition to meet her energy requirement. Taken together, it is suggested that her liver damage was primarily induced by oral intake of nutrient. Thus, import of nutrients via the portal vein or transient hyperperfusion of the liver due to demand of blood supply to the intestines might be involved in liver damage. Therefore, in the present case nutritional support through the gastrointestinal tract might have triggered the acute and severe liver injury and profound hypoglycemic coma at the same time. Throughout her clinical course, plasma glucose levels were well correlated with parameters of hepatic synthetic capacity and hepatocyte damage, such as PT-INR, AST and ALT. Thus, failure of gluconeogenesis and depletion of glycogen in the second round liver damage could be involved in severe hypoglycemia in the present case, although she was free from coma in the first round.

Regarding glucagon secretion, some reports showed that an impairment of GIP-mediated glucagon secretion could be involved in the pathogenesis of severe hypoglycemia (10) and was reversible with treatment for improvement of nutrition and weight gain (11). We did not evaluate the secretion of glucagon in the present case, but its impairment might also be involved in the episode of hypoglycemic coma, since urinary acetone or acetoacetate was negative in all of the samples.

It was reported that glycogen was accumulated in the cytoplasm in hepatocytes in a patient with kwashiorkor (12). A similar observation was reported in anorexia nervosa, and speculated to be an adaptive mechanism in carbohydrate metabolism to starvation (13), although its implication in hypoglycemia is not understood.

There was a similar case report that liver damage was found and recurrent hypoglycemic coma subsequently occurred (14). In that case, continuous infusion of 400 kcal a day had been prescribed but the patient discarded the contents of the infusion bag, and it could not be the case in the present subject. Another case of hepatic steatosis and fatal hepatic failure after total parenteral nutrition was reported, in which a hypoglycemic episode was observed (15). What was different from the present case was that total parenteral nutrition but not oral ingestion induced or worsened fatty liver changes that resulted in hepatic failure.

In conclusion, we presented a patient with anorexia nervosa who experienced hypoglycemic coma coincident with acute exacerbation of liver injury induced by oral intake of nutrient. We should be careful of severe hypoglycemia in anorexia nervosa when signs of liver damage are detected even after the patient starts oral intake of carbohydrate along with intravenous alimentation, although the precise mechanisms are yet to be clarified.

**References**


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