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Case Report

Recurrence of Hypoglycemic Coma in a Patient with Anorexia Nervosa

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Anorexia nervosa (AN) is occasionally complicated with hypoglycemic coma, which may cause sudden death by unknown mechanisms. We present the case of a 36-year-old woman with recurrent comas and a nineteen-year history of AN. She was found in a coma with remarkable hypoglycemia (28 mg/dL). Her BMI was 11.1 kg/m^2. Endocrine workup revealed extremely low serum levels of glucagon, IGF-I and insulin. Asymptomatic hypoglycemia occurred with liver injury in the refeeding process. An aberrant glucose metabolism due to liver damage might have been involved in her susceptibility to hypoglycemia. This case suggests a possible mechanism of hypoglycemic coma in AN.

Key words: anorexia nervosa, glucagon, hypoglycemic coma, insulin-like growth factor-I, liver injury

Anorexia nervosa (AN) is an eating disorder characterized by severe weight loss and malnutrition [1]. It is a comorbid disorder and has the highest mortality rate among all mental disorders [2,3]. Hypoglycemic coma in patients with AN has rarely been reported, but it is clinically important because it is potentially fatal [4-7] and its precise mechanism of onset remains unknown. We present a case of AN with recurrent hypoglycemic coma. It is interesting that serum glucagon and insulin-like growth factor-I (IGF)-I levels in this case were extremely low, indicating an impaired glucose metabolism. This case suggests that impairment of the hepatic glucose metabolism is likely to be associated with exacerbation of hypoglycemia in patients with AN.

Case Report

A 36-year-old woman with AN presented with hypoglycemic coma and was transferred to the psychiatric ward of our hospital. She had started to reduce her body weight 19 years earlier and developed amenorrhea. After she married and gave birth to a child following Kaufmann's treatment at a body weight of 42 kg eight years ago, her excessive exercise and reduction of food intake were exacerbated. She first experienced a reversible hypoglycemic coma with a blood glucose level of 12 mg/dL while doing aerobics 2 years ago, when her body weight was 28.6 kg and her body mass index (BMI) was 11.9 kg/m^2. Because she had emaciation, fear of weight gain, and body image disturbance, she was diagnosed with AN based on the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition). She experienced similar episodes of hypoglycemic coma that resulted in hospitalization five times. Her other past medical history and her familial medical history were unremarkable. Her prescribed medicines at the time of admission to our hospital were ursodeoxycholic acid (300 mg), rikkunshi-to (7.5 g), clotiaze-

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pam (5 mg) and eszopiclone (1 mg). She had no history of foods or complementary therapies that could cause hepatotoxicity.

The patient had a two-week history of general fatigue and progressive anorexia. Three days before admission to our hospital, she was found in a coma and transported to a nearby hospital. Her blood glucose level at that time was 28 mg/dL. She became alert after the intravenous administration of glucose, but her state of malnutrition was life-threatening and aggressive care was needed. She was transferred to our hospital for thorough investigation and further treatment. On admission, her height, body weight, and BMI were 155 cm, 26.7 kg, and 11.1 kg/m^2, respectively. She was drowsy and had hypothermia (body temperature of 35.2°C). Her other vital signs were as follows: blood pressure, 112/86 mmHg; heart rate, 76/min and regular; and saturation of percutaneous oxygen at room air, 94%. Physical assessment revealed anemia, dehydration, and severe emaciation, but jaundice, goiter and edema were not observed. There were no signs of respiratory or cardiac disorders.

Laboratory data showed pancytopenia with macrocytic anemia and moderately elevated serum levels of liver enzymes and metabolites, reflecting malnutrition (Table 1). An endocrine workup revealed an impaired glycometabolic system with extremely low serum levels of glucagon (< 3.5 pg/mL; normal range: 5.4-55.0) and IGF-I (< 7 ng/mL; normal range: 109-265) (Table 2). The patient's serum levels of C-peptide (0.52 ng/mL) and immunoreactive insulin (IRI; 0.7 μU/mL) were also decreased, while her serum levels of growth hormone (GH; 32.1 ng/mL), adrenocorticotropic hormone (ACTH; 22.8 pg/mL), and cortisol (23.1 μg/dL) were elevated (Table 2). The results of an electrocardiogram and a chest X-ray were normal. Ultrasonography and computed tomography (CT) showed no specific findings of the liver. There were no signs of pleural effusion or ascites. No pathological findings that might have caused a coma were detected by brain CT or magnetic resonance imaging. Electroencephalography showed that her basal brain wave was a medium alpha wave with low amplitude, and no abnormalities were detected.

Nutritional therapy including the oral ingestion of 200 kcal (29.3 g glucose, 7.5 g amino acid, and 5.6 g lipid) a day and the intravenous infusion of 1,000 mL containing 250 kcal (62.5 g glucose) for 24 h continuously with supplementation of potassium, inorganic

Table 1 Laboratory data on admission

Hematological data		Units (normal range)
White blood cells	2330 ↓	/μL (3300–8600)
Hemoglobin	10.5 ↓	g/dL (11.6–14.8)
MCV	109.9 ↑	fl (83.6–98.2)
Reticlocyte	1.30	% (0.7–2.0)
Platelets	74000 ↓	/μL (158000–348000)
Biochemical data		**Units (normal range)**
Total protein	4.9 ↓	g/dL (6.6–8.1)
Albumin	2.9 ↓	g/dL (4.1–5.1)
Prealbumin	8 ↓	mg/dL (22–40)
Blood urea nitrogen	15.1	mg/dL (8–20)
Creatinine	0.46	mg/dL (0.46–0.79)
Sodium	140	mmol/L (138–145)
Potassium	4.3	mmol/L (3.6–4.8)
Chloride	102	mmol/L (101–108)
Calcium	7.7 ↓	mg/dL (8.8–10.1)
Magnesium	1.7 ↓	mg/dL (2.0–2.5)
Inorganic phosphate	2.5 ↓	mg/dL (2.7–4.6)
Zinc	50 ↓	μg/dL (80–130)
AST	127 ↑	U/L (13–30)
ALT	81 ↑	U/L (7–23)
ALP (JSCC method)	494 ↑	U/L (106–322)
γ-GTP	74 ↑	U/L (9–32)
Total bilirubin	0.9	mg/dL (0.4–1.5)
Creatine kinase	86	U/L (41–153)
Amylase	325 ↑	mg/dL (44–132)
Cholinesterase	117 ↓	U/L (201–421)
Total cholesterol	133 ↓	mg/dL (142–248)
C-reactive protein	0.04	mg/dL (≦ 0.14)
Hemoglobin A1c	4.8 ↓	% (4.9–6.0)
Total keton bodies	24	μmol/L (0–131)
Acetoacetic acid	9	μmol/L (0–55)
3-Hydroxybutyric acid	15	μmol/L (0–85)
FFA	35 ↓	μEq/L (140–850)
Ferritin	784.0 ↑	ng/mL (6.2–138.0)
Iron	66	μg/dL (40–188)
TIBC	134 ↓	μg/dL (240–430)
UIBC	68 ↓	μg/dL (180–280)
Folic acid	7.57	ng/mL (3.89–26.8)
Vitamin B12	61297 ↑	pg/mL (197–771)
Coagulation		
PT-INR	1.19	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FFA, free fatty acid; γ-GTP, γ-glutamyl transpeptidase; JSCC method, Japan Society of Clinical Chemistry reference method; PT-INR, prothorombin time-international normalized ratio; MCV, mean corpuscular volume; TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity.

Table 2 Endocrine data before and after nutritional recovery in the patient

	Before recovery	After recovery	Units (normal range)
FPG	52	84	mg/dL (73–109)
Hormones related to glucose metabolism			
C-peptide	0.52	1.07	ng/mL (0.74–3.18)
IRI	0.7	5.2	μU/mL (2.1–19.0)
Glucagon	<3.5	7.3	pg/mL (5.4–55.0)
ACTH	22.8	23.8	pg/mL (7.2–63.3)
Cortisol	23.1	11.0	μg/dL (7.07–19.6)
GH	32.1	2.78	ng/mL (0.13–9.88)
IGF-I	<7.00	54.0	ng/mL (109–265)
Adrenaline	0.19	<0.01	ng/mL (<0.1)
Noradrenaline	0.75	0.25	ng/mL (0.1–0.5)
Dopamine	0.02	<0.01	ng/mL (<0.03)
Other hormones			
TSH	36.7	11.7	μU/mL (0.33–4.05)
FT4	0.95	0.56	ng/dL (0.97–1.69)
FT3	1.34	3.39	pg/mL (2.30–4.00)
LH	0.1	0.3	mIU/mL (1.1–12.1)
FSH	0.5	3.5	mIU/mL (2.6–11.9)
E2	<0.5	<0.5	pg/mL (28.8–196.8)
PRL	11.9	42.3	ng/mL (1.6–21.9)

The blood sampling was performed in the morning.
ACTH, adrenocorticotropic hormone; E2, estradiol; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; IGF-I, insulin-like growth factor-I; IRI, immunoreactive insulin; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.

phosphate (1,200 mg oral sodium phosphate), magnesium, and a cocktail of vitamin B was commenced. Fat emulsion, to which she had an allergy, was not used. As shown in Fig. 1, her hypoglycemia had improved 4 days after admission. However, liver injury occurred and her serum levels of aminotransferase (AST) (331 U/L) and alanine aminotransferase (ALT; 287 U/L) were elevated 3 weeks after admission (Fig. 1). Serologic tests for hepatitis B and C were negative and there was no evidence of alcohol abuse or use of hepatotoxic drugs. During the same period when the liver injury occurred, asymptomatic hypoglycemia with a blood glucose level of about 50 mg/dL was observed. The hypoglycemia improved as the liver injury was ameliorated due to refeeding. The patient's oral ingestion was then increased to 2,400 kcal a day without intravenous infusion, and nutritional therapy for 7 weeks not only improved her complicated refeeding condition but also ameliorated endocrinological suppression. Insulin secretion, the GH/IGF-I axis, and thyroid function were ameliorated (Table 2). However, the patient's intractable anorexic symptoms such as vomiting and excessive exercise interrupted body weight gain (Fig. 1). On Day 36, her body weight had decreased to 27.2 kg, although there was no clear reason for this and no use of diuretic agents had been noted. Nutritional therapy did not improve estradiol secretion possibly due to insufficient body weight gain (Table 2). The patient was discharged with a weight gain to 28.3 kg (BMI, 11.8 kg/m^2).

Discussion

Although moderate hypoglycemia in AN cases is often encountered [8], episodes of recurring hypoglycemic coma in AN patients are very rare but can be fatal [4-7]. The precise mechanism underlying the development of severe hypoglycemia in AN patients remains unclear. Of interest, the present case had an impaired hepatic glucose metabolism as indicated by undetectable glucagon and IGF-I levels. Moderately elevated levels of hepatic enzymes were also observed, reflecting liver injury due to malnutrition [9,10]. During the

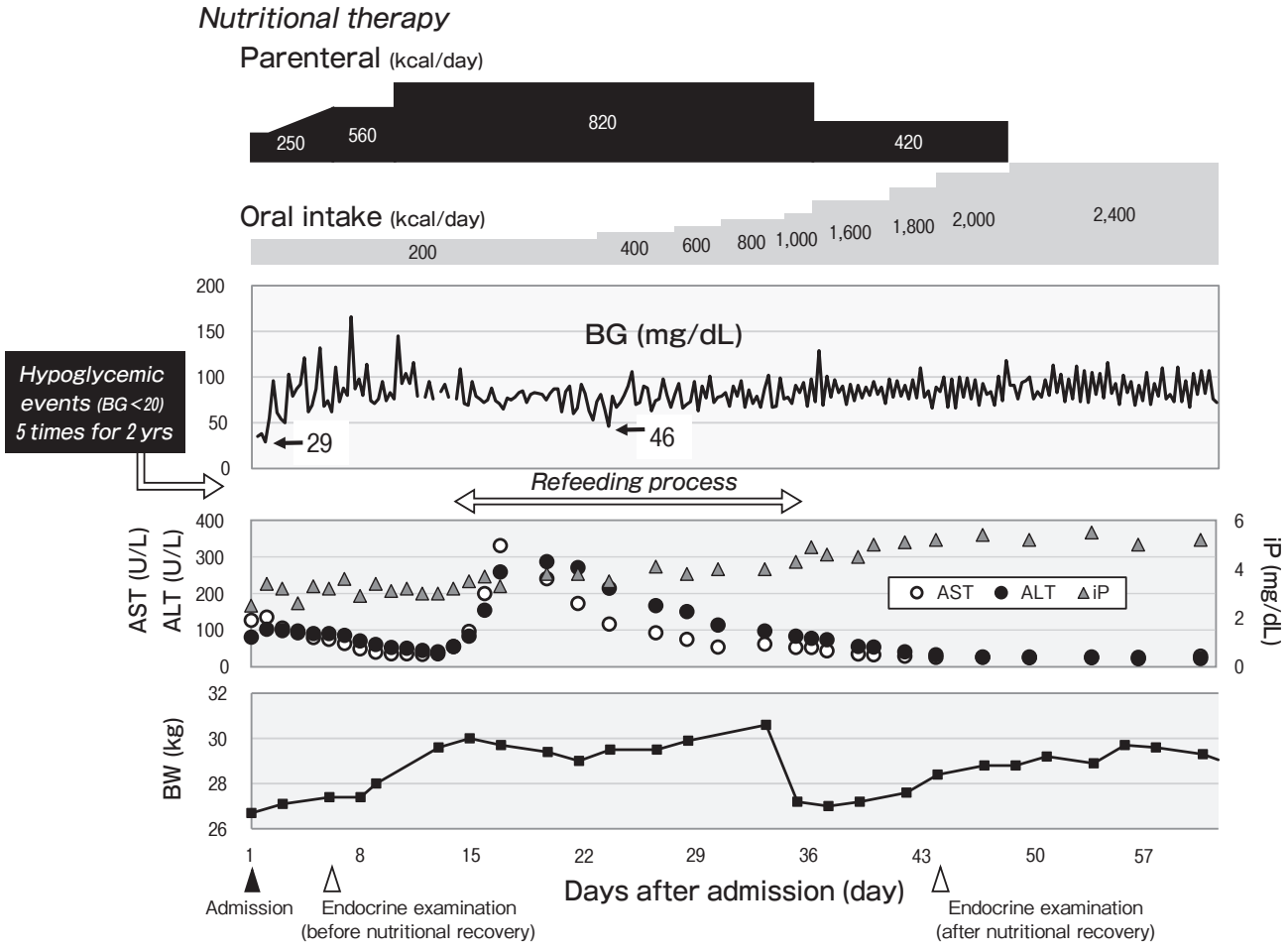

Fig. 1 Clinical course. Hypoglycemic events (BG <20 mg/dL) occurred 5 times over the 2-year period before admission. Asymptomatic hypoglycemia on admission was treated by nutritional supplementation. After transient increases in serum AST and ALT levels, hypoglycemia and liver function gradually improved with continued nutritional rehabilitation. Endocrine tests were performed on the indicated dates; the results are shown in **Table 2**. ALT, alanine aminotransferase; AST, aminotransferase; BG, blood glucose; BW, body weight; iP, inorganic phosphate.

patient's clinical course, her liver injury was exacerbated in the refeeding process with asymptomatic hypoglycemia (Fig. 1). After she had recovered from the liver injury and malnutrition, she no longer presented with hypoglycemia and her endocrinological abnormality including extremely decreased levels of serum glucagon and IGF-I was reversed, suggesting that the primary cause of the hypoglycemia was related to her liver damage (Table 2).

Regarding the pathophysiology of hypoglycemic coma in AN patients, previous studies have suggested several different mechanisms, including impaired gluconeogenesis due to infection [11] or liver injury [9,10,12-14], insufficient glucagon function [15-17], lack of glucose and lipid accumulation [7,18], and reactive hypoglycemia [19-21]. Patients with AN also tend to manifest starvation-induced hepatitis, which is a high risk for hypoglycemia and can be fatal due to depleted glycogen stores and impaired gluconeogenesis in severe cases [8,10,22]. In addition, since our patient experienced recurrent hypoglycemia, hypoglycemia-associated autonomic failure (HAAF) might have contributed to her particular pathology [23]. HAAF is typically seen in diabetic patients with a compromised defense against hypoglycemia, and those patients are unaware of hypoglycemia with a lack of glucose counter-regulations including glucagon secretion [23].

Excessive activation of liver autophagy is a key con-

tributor to liver dysfunction in people in a starved condition [24]. On the other hand, during the refeeding process, elevated serum levels of aminotransferases in AN patients are considered to be due to hepatic steatosis [25]. Imaging tests such as ultrasound (US) and CT are useful for determining whether liver dysfunction is caused by starvation or refeeding [26]. The present case showed bimodal elevations of transaminases on admission and in the refeeding period, as shown in Fig. 1. Since US on admission showed no signs of fatty liver, her liver dysfunction was considered to be due to starvation at that time, while the liver injury during the refeeding process was thought to have been caused by refeeding syndrome. Also, carnitine deficiency could have been involved in the deterioration of hypoglycemia before and after the commencement of nutritional therapy [27, 28]. The present case showed no clear evidence of the development of an infectious disease or reactive hypoglycemia, but did show liver injury, aberrant hepatic glycometabolism, and lack of glucose and lipid accumulation.

Regarding endocrine characteristics in our patient (Table 2), hypercortisolemia (increased ACTH and cortisol secretion), GH resistance (low IGF-I and increased GH), and hypogonadotropic hypogonadism (low follicle-stimulating hormone and luteinizing hormone levels) were present, suggesting underlying severe malnutrition consistent with AN [29]. The hypothalamic-pituitary-adrenal axis is chronically stimulated due to the stress of starvation in anorectic patients, and cortisol works as a counter-regulatory hormone to hypoglycemia [29, 30]. Another hormone acting in a counter-regulatory way to insulin is catecholamine, whose turnover is impaired primarily in patients with AN [31], while those hormones were slightly elevated in our case. An examination of our patient's thyroid function showed an inappropriately increased level of thyroid-stimulating hormone (TSH) with low levels of free triiodothyronine (T3) and free thyroxine; these findings are inconsistent with a typical state of malnutrition [29]. Since serum anti-thyroid peroxidase and anti-thyroglobulin antibodies were negative, her hypothyroidism was presumed to be caused by silent thyroiditis and/or low T3 syndrome associated with an inappropriately high secretion of TSH [32]. In addition, iodine deficiency due to anorexia might have been involved in the development of hypothyroidism, though urinary iodine excretion was not evaluated in this case.

It is noteworthy that both glucagon secretion and insulin secretion are impaired in anorectic patients [17]. Glucagon is known to have the capabilities of hepatic gluconeogenesis, glycogenolysis, and glucose tolerance. It has been shown that the recovery of plasma glucose levels from insulin-induced hypoglycemia is impaired in AN patients due to insufficient glucagon secretion and that recovery is possible by nutritional treatment [15]. It has also been reported that patients with AN had greatly reduced sensitivity in glucagon-induced hepatic glycogenolysis [16]. The GH/IGF-I axis depends mainly on nutritional status. Undernutrition induces GH resistance, which is reversed by refeeding and weight recovery [29]. GH elevation may serve to maintain euglycemia by gluconeogenesis and lipolysis [29].

In summary, we have presented a case of AN with recurrent hypoglycemic coma. The patient had reversible asymptomatic hypoglycemia coincident with liver injury and an aberrant hepatic glucose metabolism, which were considered to have played a key role in the induction of hypoglycemia. Of note, it was conceivably an important factor in the patient's susceptibility to hypoglycemia that she had a very low BMI and a long-term state of malnutrition, inducing the lack of glucose and lipid accumulation. This case suggests a possible underlying mechanism of the development of hypoglycemic coma in patients with AN, although the detailed mechanism has yet to be elucidated. Clinicians should pay particular attention to asymptomatic hypoglycemia, especially when there is hepatic damage, in anorectic patients.

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