Endocrinology, Diabetes & Metabolism CASE REPORTS

T Anno and others | Hypoglycemia triggered by liver injury

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Hypoinsulinemic hypoglycemia triggered by liver injury in elderly subjects with low body weight: case reports

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Summary

Hypoglycemia is induced by many causes, especially over-dose of insulin or oral hypoglycemic agents in diabetic subjects. In such a case, hyperinsulinemic hypoglycemia is usually observed. On the other hand, it is important to classify secondary hypoglycemia and hypoinsulinemic hypoglycemia. Liver injury-induced hypoglycemia is one of the causes of hypoinsulinemic hypoglycemia but rarely observed in clinical practice. Herein, we experienced similar 2 cases of non-diabetic hypoinsulinemic hypoglycemia. Both of them were elderly subjects with low body weight. Furthermore, it is likely that hypoinsulinemic hypoglycemia in both subjects was triggered by severe liver injury, at least in part, due to possible limited liver glycogen store. In elderly subjects with low body weight and/or malnutrition, metabolism in the liver is reduced and glycogen accumulation is decreased. Such alteration brings out acute and marked liver injury, which finally leads to the onset of severe hypoglycemia. It is known that not only liver injury but also multiple organ failure could be induced due to extreme emaciation in subjects. It is likely that in elderly subjects with low body weight and/or malnutrition, multiple organ failure including liver failure could be induced due to the similar reason. Therefore, we should be very careful of such subjects in order to avoid the development of multiple organ failure which leads to life-threatening situations. In conclusion, we should keep in mind the possibility of hypoinsulinemic hypoglycemia when we examine severe liver injury, especially in elderly or starving subjects with low body weight and limited liver glycogen stores.

Learning points:

- It is important to classify secondary hypoglycemia and hypoinsulinemic hypoglycemia.
- Liver injury-induced hypoglycemia is one of the causes of hypoinsulinemic hypoglycemia but rarely observed in everyday clinical practice.
- Herein, we reported similar 2 cases of hypoinsulinemic hypoglycemia without diabetes presumably triggered by severe liver injury.
- In both cases, hypoglycemia was improved by glucose infusion, although their liver injury was not improved.
- We should keep in mind the possibility of hypoinsulinemic hypoglycemia when we examine severe liver injury, especially in elderly subjects with low body weight.

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Background

Hypoglycemia is induced by many causes, especially over-dose of insulin or oral hypoglycemic agents in diabetic subjects. In such a case, hyperinsulinemic hypoglycemia is usually observed. On the other hand, it is difficult to diagnose hypoinsulinemic hypoglycemia, which is sometimes observed in adult non-diabetic subjects (1, 2). Liver injury is one of the causes of hypoglycemia. The major case of acute liver failure is hepatitis virus infection or drug-induced liver damage, but in many cases, the cause of liver failure remains unknown (3). Liver injury-induced hypoglycemia is thought to show hypoinsulinemic hypoglycemia but rarely observed in clinical practice. However, recently, we experienced 2 similar cases of elderly subjects with hypoinsulinemic hypoglycemia both of which were presumably triggered by severe liver injury. These cases are very rare, and there were many similarities between these 2 cases.

Case presentation

Case 1 was an 83-year-old woman who had old cerebral infarction and Alzheimer dementia treated with rivastigmine and was admitted to our hospital due to coma, hypothermia and hypoglycemia. Three days before she started having therapy with sulbactam/ampicillin for pneumonia. Case 2 was a 79-year-old man who had hypertension treated with irbesartan/amlodipine and dementia with Lewy bodies treated with donepezil hydrochloride and was admitted to our hospital due to coma, hypothermia and hypoglycemia. From 1 month before, he had suffered from repeated aspiration pneumonia.

Body weight and BMI in both cases were very low. Height, body weight, BMI in case 1 and case 2 were 140.0 cm, 31.9 kg, 16.3 kg/m^2 and 159.0 cm, 39.0 kg, 15.4 kg/m^2, respectively. On admission, body temperature, blood pressure, heart rate, saturation of arterial blood oxygen in case 1 and case 2 were 34.9°C, 107/58 mmHg, 41 beats/min, 97.0% and 34.0°C, 92/76 mmHg, 89 beats/min, 93.0%, respectively. Table 1 shows clinical characteristics and results of biochemical studies in 2 cases. Both cases showed hypoinsulinemic hypoglycemia. Plasma glucose (PG) level in case 1 was as low as 10 mg/dL. Serum insulin and C-peptide levels in case 1 were as low as <1.0 μU/mL and 0.1 ng/mL, respectively. Similarly, PG level in case 2 was as low as 37 mg/dL. Serum insulin and C-peptide levels in case 2 were also as low as <1.0 μU/mL and 0.3 ng/mL, respectively. In addition, both cases had very severe liver injury as follows: (case 1) T-Bil: 1.7 mg/dL U/L; AST: 1102 U/L; ALT: 401 U/L; ALP: 2113 U/L; γ-GTP: 88 U/L; LDH: 704 U/L; (case 2) T-Bil: 2.2 mg/dL U/L; AST: 2363 U/L; ALT: 1797 U/L; ALP: 4068 U/L; γ-GTP: 101 U/L; LDH: 1040 U/L (Fig. 1). In both cases, HBs antigen, HCV antibody and antinuclear antibody were negative. Inflammation markers were as follows: (case 1) WBC: 15 250/μL; Neut: 92.0%; CRP: 0.64 mg/dL; (case 2) WBC: 20 820/μL; Neut: 90.3%; CRP: 2.21 mg/dL. Anemia was observed in both cases: (case 1) RBC: 277 × 10^4/μL, Hb: 8.5 g/dL; (case 2) RBC: 333 × 10^4/μL, Hb: 10.5 g/dL, but fecal Hb was negative and renal function was normal. Chest and abdominal computed tomography and abdominal ultrasonography revealed inflectional area of chest, a little of pleural effusion and ascites in both cases (Fig. 2). In such image inspection, there was no lesion indicating malignancy. Both cases did not have hypoglycemia or liver dysfunction 1–2 months before. Laboratory data 2 months before in case 1 were as follows: PG: 129 mg/dL; HbA1c: 4.9%; AST: 14 U/L; ALT: 7 U/L; γ-GTP: 20 U/L; LDH: 238 U/L. Laboratory data 1 month before in case 2 were as follows: PG: 98 mg/dL; AST: 18 U/L; ALT: 24 U/L; γ-GTP: 12 U/L; LDH: 191 U/L.

Table 2 shows time course of various clinical data in both cases. Because of various findings including low NH_3 levels (48 μg/dL in case 1 and 37 μg/dL in case 2), prothrombin activity (43.8% and 60.9%), PT-INR (1.50 and 1.27), we could not diagnose these patients as acute liver failure or fulminant hepatic failure with confidence. In both cases, the cause of liver injury remained unknown. In both cases, hypoglycemia was improved with intravenous glucose injection and subsequent continuous glucose infusion, but their liver injury was not improved in both cases. Fifteen days and thirteen days after the admission, case 1 and case 2 died of multiple organ failure including liver injury (Fig. 1).

Discussion

As a cause of hypoglycemia, there are mainly 2 types: hyperinsulinemic hypoglycemia and hypoinsulinemic hypoglycemia. Hyperinsulinemic hypoglycemia is usually observed after over-dose of insulin or oral hypoglycemic agents in diabetic subjects. In such a case, hypoglycemia is caused by hyperinsulinemia or exaggerated insulin action. On the other hand, hypoinsulinemic hypoglycemia is mainly caused by reduction of glycogenolysis and/or gluconeogenesis and consequent decrease of blood glucose levels. Furthermore, in both cases with hyperinsulinemic or hypoinsulinemic hypoglycemia

Table 1 Clinical characteristics of 2 cases with hypoinsulinemic hypoglycemia triggered by severe liver injury.

	Normal range	Case 1	Case 2
Age (years old)		83	79
Gender		female	male
Height (cm)		140.0	159.0
Body weight (kg)		31.9	39.0
Body mass index (kg/m2)		16.27	15.43
Red blood cell count (x104 /μL)	435–555	277	333
Hemoglobin (g/dL)	13.7–16.8	8.5	10.5
White blood cell count (/μL)	3300–8600	15250	20820
Neutrophil (%)	52.0–80.0	92.0	90.3
Lymphocyte (%)	20.0–40.0	6.0	7.9
Platelet (x104 /μL)	15.8–34.8	22.4	6.7
C-reactive protein (mg/dL)	<0.14	0.64	2.21
Plasma glucose level (mg/dL)		10	37
IRI (μU/mL)	0.0–10.0	<1.0	<1.0
C-peptide levels (ng/mL)	0.8–2.5	0.1	0.3
HbA1c (4.9 – 6.0 %)		4.9	5.7
Adrenocorticotropic hormone (pg/mL)	7.2–63.2	26.9	2.2
Cortisol (μg/dL)	4.5–21.1	72.6	69.3
Growth hormone (μIU/mL)		29.58	6.93
Insulin-like growth factor 1 (ng/mL)		≤10	≤10
Total Bilirubin (mg/dL)	0.4–1.5	1.7	2.2
Aspartate aminotransferase (U/L)	13–30	1102	2363
Alanine aminotransferase (U/L)	10–42	401	1797
Alkaline phosphatase (U/L)	106–322	2113	4068
Gamma-glutamyltransferase (U/L)	13–64	88	101
Lactate dehydrogenase (U/L)	124–222	704	1040
Ammonia (μg/dL)	12–66	48	37
Hepatitis A virus antibody, immunoglobulin M		0.16 (–)	N/A
Quantitation of hepatitis B virus DNA (LC/mL)		n.d.	n.d.
Hepatitis C virus antibody		0.2 (–)	0.1 (–)

N/A, not applicable; n.d., not detected.

when glucose levels are decreased, several stress responses occur to maintain the normoglycemic state. For example, insulin secretion is reduced and various counter regulatory hormones such as glucagon are increased, which leads to glycogenolysis and gluconeogenesis. Hypoglycemia occurs when gluconeogenesis fails, especially in cases of severe malnutrition such as anorexia nervosa patients with decreased liver glycogen stores (4). Similarly, malnutrition with elderly or starving subjects also seemed to be status of gluconeogenesis failure and low glycogen stores. It is known that insufficiency or deficiency of various counter regulatory hormones against hypoglycemia further facilitates hypoinsulinemic hypoglycemia. Therefore, it is important to classify secondary hypoglycemia (5) and hypoinsulinemic hypoglycemia (1, 2). Herein, we reported 2 similar cases of non-diabetic hypoinsulinemic hypoglycemia patients with severe liver injury. In both cases, patients were elderly subjects with dementia and low body weight. However, they did not have hypoglycemia or liver injury one or two month before. Since both cases suffered from pneumonia, there is a possibility that pneumonia and/or drug were involved in the onset of hypoglycemia and liver injury. We think that hypoglycemia was associated with severe liver injury in both cases. They did not have renal failure and did not taken oral drugs which could induce hypoinsulinemic hypoglycemia. Moreover, their laboratory analyses revealed that both patients did not suffer from hypopituitarism, adrenal insufficiency and hypothyroidism. Both subjects had medical history of dementia and were in low nutritional status. They were elderly subjects with low body weight and, although speculative, with possible limited liver glycogen stores. In such a case, we have to consider Kwashiorkor-type malnutrition (6, 7). It is known that Kwashiorkor-type malnutrition also causes fatty liver and/or liver dysfunction same as anorexia nervosa. Although our cases did not have fatty liver in the abdominal ultrasonography and computed tomography, it is possible that our cases suffered from Kwashiorkor-type malnutrition. Taken together, we assume that their hypoinsulinemic hypoglycemia was induced by severe liver injury in both

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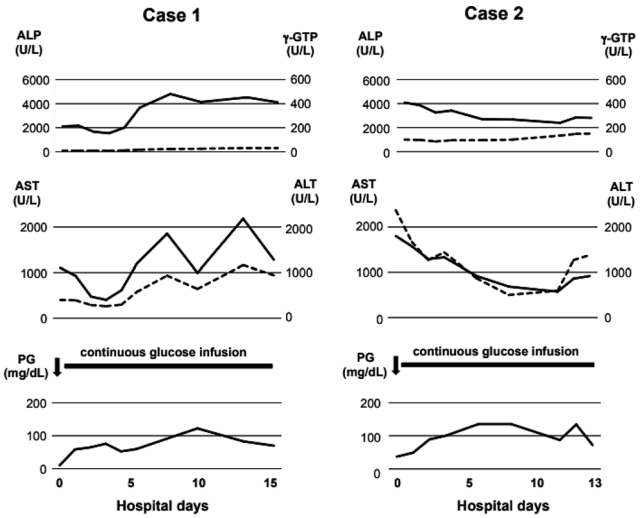

Figure 1
Clinical time course in case 1 and case 2: hypoglycemia and liver injury were observed on admission. Their hypoglycemia was improved with intravenous glucose injection and subsequent continuous glucose infusion, but their liver injury was not improved in both cases.

elderly subjects with low body weight. Unfortunately, liver biopsies were not done in both cases. However, we think malnutrition were, at least in part, associated with liver failure.

Another problem was causes of severe liver injury. On admission, there was not enough information with which we could diagnose them as acute liver failure or

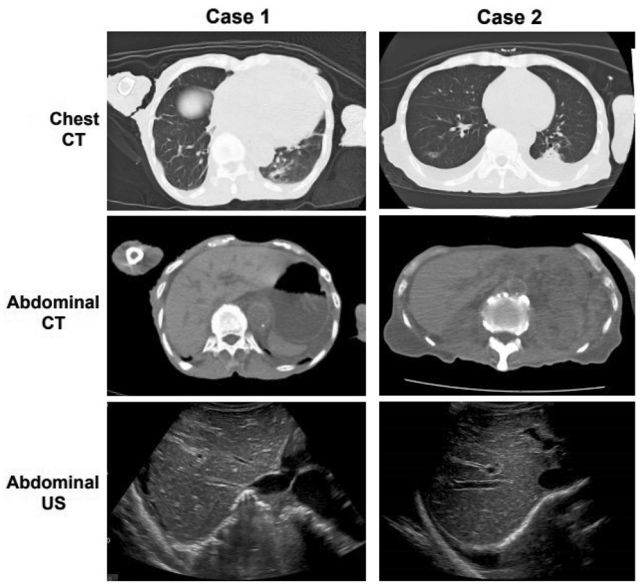

Figure 2
Chest computed tomography (CT), abdominal CT and abdominal ultrasonography (US) in case 1 and case 2: in both cases, chest and abdominal computed tomography revealed inflectional area of chest, a little of pleural effusion and ascites.

Table 2 Time course of liver injury and undernutrition.

	Day 1	Day 6	Day 10*
Case 1			
T-BIL (mg/dL)	1.7	2.0	3.3
AST (U/L)	1102	1192	993
ALT (U/L)	401	576	643
ALP (U/L)	2113	3661	4132
γ-GTP (U/L)	88	162	247
LDH (U/L)	704	893	867
NH_3 (μg/dL)	48		
PA (%)	43.8	66.0	61.7
PT-INR	1.50	1.22	1.26
WBC count (/μL)	15250	8200	4030
Lymphocyte (%)	6.0	8.0	9.0
Platelet (x104 /μL)	22.4	9.7	6.1
Albumin (g/dL)	3.7	3.1	3.1
Cholinesterase (IU/L)	178	156	165
Case 2			
T-BIL (mg/dL)	2.2	1.4	1.4
AST (U/L)	2363	865	594
ALT (U/L)	1797	917	572
ALP (U/L)	4068	2695	2390
γ-GTP (U/L)	101	94	132
LDH (U/L)	1040	624	656
NH_3 (μg/dL)	37		
PA (%)	60.9	60.9	67.8
PT-INR	1.27	1.27	1.21
WBC count (/μL)	20820	7560	2420
Lymphocyte (%)	7.9	11.0	17.0
Platelet (x104 /μL)	67	20	46
Albumin (g/dL)	2.2	1.7	1.8
Cholinesterase (IU/L)	108	91	95

*Data presented is Day 11 for Case 2.
T-BIL, totla bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, gamma glutamyltransferase; LDH, lactate dehydrogenase; NH3, ammonia; PA, prothrombin activity; INR-PT, international normalized ratio of prothrombin time; WBC, white blood cells.

fulminant hepatic failure, because of their normal range of NH3 levels, PT-INR ≤1.5 and PT activity >40%, even within 8 weeks of the first symptoms. It is known that major case of acute liver failure is hepatitis virus infection or drug-induced liver damage. In our cases, however, hepatitis virus was not detected, and there was no possible drug that induces liver damage before admission to our hospital. While in many cases the cause of liver failure remains unknown, the cause of severe liver injury in our cases also remained unknown. Unfortunately, in both cases, they died of multiple organ failure including severe liver injury in spite of the improvement of hypoglycemia by continuous glucose infusion.

The most important message, which we would like to convey through this manuscript is as follows: in elderly subjects with low body weight and/or malnutrition, metabolism in the liver is reduced and glycogen

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accumulation is decreased. Such alteration brings out acute and marked liver injury which finally leads to the onset of severe hypoglycemia. Therefore, in case of hypoinsulinemic hypoglycemia, we should keep in mind the possibility that such hypoinsulinemic hypoglycemia is induced by severe liver injury. It is known that not only liver injury but also multiple organ failure could be induced due to extreme emaciation in subjects (e.g. subjects with anorexia nervosa). It is likely that in elderly subjects with low body weight and/or malnutrition, multiple organ failure including liver failure could be induced due to the similar reason. Therefore, we should be very careful of such subjects in order to avoid the development of multiple organ failure which leads to life-threatening situations.

In conclusion, we should keep in mind the possibility of hypoinsulinemic hypoglycemia when we examine severe liver injury, especially in elderly or starving subjects with low body weight and limited liver glycogen stores.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
First case (the patient died): Informed consent for publication of this case report and any accompanying images was obtained from the patient's next-of-kin (her daughter). A copy of the consent is available for review by the Editor-in-Chief of this journal. Second case (the patient died): Informed consent for publication of this case report and any accompanying images was obtained from the patient's next-of-kin (his wife). A copy of the consent is available for review by the Editor-in-Chief of this journal.

Author contribution statement
T A and H K researched data and wrote the manuscript. R S, F K, Y K and N U researched data and contributed to the discussion. H K, K K and N O reviewed the manuscript.

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