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Case Report

Recurrent Hypoglycemic Coma Episodes Associated With Primary Biliary Cirrhosis

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Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by interlobular bile duct inflammation, which causes fibrosis and cirrhosis. Few studies have explored the association of hypoglycemia with PBC. In this case, a 76-year-old Chinese man diagnosed with PBC developed recurrent comatose episodes. The patient had severe hypoglycemia and slight abnormalities in liver function tests. In addition, the patient had positive results in antimitochondrial antibody, anti-mitochondrial antibody-subtype 2, centromeric protein B antibody, and antisoluble acidic nuclear protein 100 antibody levels, which led to the diagnosis of PBC. The patient also experienced fasting hypoglycemic coma, requiring thorough evaluation to identify potential causes. This case suggests that liver-derived hypoglycemia associated with PBC may be more common than autoimmune-related hypoglycemia in this context.

Key Words: primary biliary cirrhosis, recurrent altered consciousness, hyperinsulinemic hypoglycemia, liver-derived hypoglycemia, case report

Abbreviations: AIH, autoimmune hepatitis; AMA, antimitochondrial antibody; IAS, insulin autoimmune syndrome; PBC, primary biliary cholangitis.

Introduction

Primary biliary cholangitis (PBC) is a relatively rare chronic autoimmune disease that is commonly detected in women at age 40 to 50 years [1]. In China and Japan, the reported prevalence of PBC in adults is 49/100 000 and 55/100 000 [2], respectively, with most patients presenting with antimitochondrial antibodies (AMA). The symptoms of PBC include fatigue, pruritus, concurrent autoimmune diseases, and metabolic abnormalities. PBC can progress to cirrhosis and liver failure, requiring liver transplantation in some cases [3]. PBC-related hypoglycemia, with atypical manifestations, is rare and easily missed in clinical practice [4]. To date, only 3 cases have been reported, 2 linked to insulin autoimmune syndrome (IAS) [5, 6] and 1 to autoimmune hepatitis (AIH) [7]. In this report, we describe a 76-year-old Chinese man with recurrent episodes of altered consciousness, initially suspected to be related to epilepsy. However, it was subsequently confirmed to be associated with reoccurring episodes of hypoglycemic coma related to PBC.

Case Presentation

A 76-year-old Chinese man presented with a sudden loss of consciousness without prodromal symptoms. The episode lasted for approximately 2 hours and resolved before the patient presented to the local hospital. He later experienced recurrent episodes of altered consciousness (lasting about 30 minutes each time) resulting from irregular breakfast intake. The patient regained consciousness without discomfort after eating and sought medical attention at a tertiary hospital, where a preliminary diagnosis of possible epilepsy was made. However, his symptoms persisted despite 1 month of antiepileptic treatment, leading him to discontinue the medication. Six months later, the patient experienced another prolonged episode of unconsciousness and was taken to the local hospital, where his blood glucose was found to have decreased to 2.32 mmol/L (41.76 mg/dL) (normal reference range: 3.89-6.11 mmol/L; 70-110 mg/dL). Intravenous glucose infusion resulted in gradual recovery of consciousness. Further examination via head magnetic resonance imaging and magnetic resonance angiography revealed segmental stenosis resulting from cerebral arterial sclerosis. The patient's blood biochemistry showed a fasting blood glucose level of 2.41 mmol/L (43.38 mg/dL) (normal range: 3.89-6.11 mmol/L; 70-110 mg/dL). Given that the cause of consciousness loss and hypoglycemia was unclear, he was transferred to the neurology department for further evaluation and management. Notably, the patient reported no significant medical history besides the recurrent episodes of altered consciousness. Additional laboratory tests revealed a fasting blood glucose level of 2.79 mmol/L (50.22 mg/dL), insulin level of 8.3 μU/mL (49.8 pmol/L) (normal reference range: 1.8-11.8 μU/mL; 10.8-70.8 pmol/L), and C-peptide level of 1.76 ng/mL (0.59 nmol/L) (normal reference range: 0.78-5.19 ng/mL; 0.26-1.73 nmol/L). The hemoglobin A1c level was 5.7% (39 mmol/mol) (normal reference range: 5%-6.4%; 31-46 mmol/mol). He denied history of thyroid disease, malignant tumor, or diabetes. Alcohol and acetaminophen levels

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Table 1. Oral glucose tolerance tests and insulin–C-peptide release tests

Time (h)	Glucose (mmol/L)/(mg/dL)	Insulin[a] (μU/mL)/(pmol/L)	C-peptide (ng/mL)/ (nmol/L)	Insulin release index	Insulin release correction index	Insulin/ C-peptide molar ratio
Normal reference range	3.89-6.11 mmol/L; 70-110 mg/dL	1.8-11.8 μU/mL; 10.8-70.8 pmol/L	0.78-5.19 ng/mL; 0.26-1.73 nmol/L			
0	3.55 mmol/L/64 mg/dL	19.8 μU/mL/118.8 pmol/L	3.82 ng/mL/1.27 nmol/L	0.31	58.41	0.10
Postload 1 h	7.48 mmol/L/135 mg/dL	31.9 μU/mL/191.4 pmol/L	7.54 ng/mL/2.51 nmol/L	0.24	30.62	0.08
Postload 2 h	7.55 mmol/L/135 mg/dL	52.2 μU/mL/313.2 pmol/L	10.66 ng/mL/3.55 nmol/L	0.38	49.59	0.10
Postload 3 h	6.26 mmol/L/113 mg/dL	54.7 μU/mL/328.2 pmol/L	9.73 ng/mL/3.24 nmol/L	0.49	66.18	0.11
Postload 4 h	3.48 mmol/L/63 mg/dL	27.0 μU/mL/162.0 pmol/L	7.4 ng/mL/2.47 nmol/L	0.43	82.62	0.07
Postload 5 h	1.86 mmol/L/34 mg/dL	13.3 μU/mL/79.8 pmol/L	4.47 ng/mL/1.49 nmol/L	0.40	381.71	0.06

[a]Insulin tested using the chemiluminescence method.

Table 2. Diabetes-related autoantibody profile

Diabetes-related autoantibody profile	Detection method	Result	Reference
Glutamic acid decarboxylase antibody	Chemiluminescence method immunoblotting	<2.5 U/mL Negative(−)	<10 U/mL Negative(−)
Insulin autoimmune antibodies	radioligand method Chemiluminescence method	<0.1 U/mL Negative(−)	0-0.40 U/mL Negative(−)
Anti-islet cell antibodies	Immunoblotting Chemiluminescence method	Negative(−) Negative(−)	Negative(−) Negative(−)
Tyrosine phosphatase antibody	Radioligand method	0.1 U/mL	Negative(0-1 U/mL)critical value(1-2 U/mL) positive(≥2 U/mL)
Zinc transporter-8 antibody	Immunoblotting	Negative(−)	Negative(−)

Table 3. Cortisol rhythm, glucagon, IGF-1, and GH

Cortisol rhythm	Cortisol (μg/dL)/(nmol/L)	ACTH (pg/mL)/(pmol/L)
Normal reference range	At 8:00: 4.82-19.5 μg/dL, 133-538 nmol/L; at 16:00 2.47-11.9 μg/dL, 68-328 nmol/L	At 8:00:7.2-63.3 pg/mL; 1.6-13.9 pmol/L
0:00	4.45 μg/dL/123 nmol/L	7.04 pg/mL/1.55 pmol/L
8:00	10.20 μg/dL/281 nmol/L	7.42 pg/mL/1.63 pmol/L
16:00	4.04 μg/dL/112 nmol/L	6.74 pg/mL/1.48 pmol/L
Parameter	**Result**	**Reference Range**
24-h urinary free cortisol	87.2 nmol/24 h	11.8-485.6 nmol/24 h
Glucagon (ELISA)	3.96 pmol/L (13.87 ng/mL)	1.5-18.0 pmol/L (5.22- 62.68 ng/mL)
IGF-1 (ELISA)	207 ng/mL (27.13 nmol/L)	71-234 ng/mL (9.30-30.66 nmol/L)
GH (ELISA)	0.16 ng/mL	0.01-2.47 ng/mL

Table 4. Blood and urine catecholamine measurement

Parameter	Blood	Reference range	Urine(volume 1900 mL)	Reference range
3-Methoxytyramine	<24 pmol/L	≤100.0 pmol/L	139.8 nmol/24 h	<382.0 nmol/24 h
Methoxyadrenaline	80.5 pmol/L	≤420.9 pmol/L	73.1 nmol/24 h	<216.0 nmol/24 h
Methoxynoradrenaline	299.2 pmol/L	≤709.7 pmol/L	53.7 nmol/24 h	<312.0 nmol/24 h
Dopamine	43.9 pmol/L	<196.0 pmol/L	1338.2 nmol/24 h	750-2088 nmol/24 h
Epinephrine	<22 pmol/L	≤605.9 pmol/L	16.7 nmol/24 h	4.3-61.6 nmol/24 h
Norepinephrine	467.7 pmol/L	413.9-4434.2 pmol/L	82.2 nmol/24 h	60.0-352.0 nmol/24 h

were negative, α-fetoprotein was normal, and hepatitis B and C serological tests were negative. The patient denied history of hypoglycemic agents or exogenous insulin use, as did his cohabitants. Given the complexity of the present case, the patient was referred to the endocrinology department.

Diagnostic Assessment

Upon admission to our department, the patient's mental status and appetite was normal. His sleep pattern and weight were all normal. He reported a lifelong habit of skipping breakfast. During hospitalization, the patient frequently experienced asymptomatic fasting hypoglycemia, with lowest glucose recorded being 2.86 mmol/L (51 mg/dL), which resolved after eating food. A 75-g prolonged oral glucose tolerance test and insulin, C-peptide release test showed plasma glucose concentration of 1.86 mmol/L (34 mg/dL), with an insulin level of 13.3 μU/mL (79.8 pmol/L) and C-peptide of 4.47 ng/mL (1.49 nmol/L) (Table 1), suggesting hypoglycemia induced by endogenous hyperinsulinism [8]. Qualitative tests including chemiluminescence immunoassay and radioimmunoassay for insulin auto-antibody (IAA) and glutamic acid decarboxylase antibodies, respectively, obtained negative results (Table 2). Although there was a relatively high level of endogenous insulin secretion, the levels of counterregulatory hormones (including cortisol, GH, IGF-1, glucagon, and catecholamines and their metabolites) were not significantly elevated. Further analysis revealed that the thyroid, parathyroid, and reproductive hormones were within reference ranges, and blood and urine ketones were negative (Table 3 **and** Table 4).

Considering the manifestation of hyperinsulinemic hypoglycemia (Table 5) in the absence of a history of diabetes, oral hypoglycemic agent use, or history of gastrointestinal surgery, as well as the absence of circulating insulin antibodies, we further examined the presence and location of insulinoma, a condition that affects approximately 1 in 250 000 patient-years [9]. Transabdominal ultrasound showed slightly coarse liver echo but normal pancreatic size, shape, and blood flow. Enhanced abdominal magnetic resonance imaging and computed tomography scans revealed early signs of liver cirrhosis, mild dilation of the main pancreatic duct, and multiple renal cysts, whereas endoscopic ultrasonography showed no pancreatic lesions.

Reevaluation results indicated that the transaminase levels were within the normal range, alkaline phosphatase exhibited mild elevation at 139 U/L (normal reference range: 30-120 U/L). The concentration of γ-glutamyl transpeptidase was twice (125 U/L) the upper limit of the normal range (normal reference range: 8-57 U/L). Strong positive results (+++) were obtained for AMA and AMA-subtype 2, centromeric protein B antibody, as well as antisoluble acidic nuclear protein 100 (SP100) antibody. The antinuclear antibodies titer was 1:320. These results collectively led to a diagnosis of PBC [3]. The patient was informed about the need for a liver tissue biopsy and provided written informed consent. Pathological staging confirmed stage III. Hematoxylin and eosin staining showed mild disturbance in the lobular architecture, along with occasional focal necrosis. Minimal sinusoidal dilation and a light infiltration of mononuclear cells were noted. In addition, mild inflammatory infiltration, primarily by mononuclear cells, and mild interface hepatitis were seen in some portal areas. Furthermore, fibrous tissue proliferation was detected in the portal areas, leading to bridging fibrous septa. Cytokeratin 19 staining confirmed reduced or absent bile

Table 5. Hyperinsulinemic hypoglycemia

	Exogenous insulin	Insulin secretagogues	Insulinoma	Noninsulinoma pancreatogenous hypoglycemia syndrome	Insulin autoimmune syndrome	Type B insulin resistance	Reactive hypoglycemia	Dumping syndrome
Insulin	>>3 μU/mL (18 pmol/L)	≥3 μU/mL (18 pmol/L)	≥3 μU/mL (18 pmol/L)	≥3 μU/mL (18 pmol/L)	>>3 μU/mL (18 pmol/L)	≥3 μU/mL (18p mol/L)	≥3 μU/mL (18 pmol/L)	≥3 μU/mL (18 pmol/L)
C-peptide	<0.6 ng/mL (0.2 nmol/L)	≥0.6 ng/mL (0.2 nmol/L)	≥0.6 ng/mL (0.2 nmol/L)	≥0.6 ng/mL (0.2 nmol/L)	>>0.6 ng/mL (0.2 nmol/L)	≥0.6 ng/mL (0.2 nmol/L)	≥0.6 ng/mL (0.2 nmol/L)	≥0.6 ng/mL (0.2 nmol/L)
Clinical manifestation	drug history	drug history	Fasting hypoglycemia	Postprandial hypoglycemia	History of sulfhydryl drugs, fasting or postprandial hypoglycemia	Postprandial hypoglycemia, Acanthus nigricans	Prediabetes; postprandial hypoglycemia	History of gastrointestinal surgery postprandial hypoglycemia

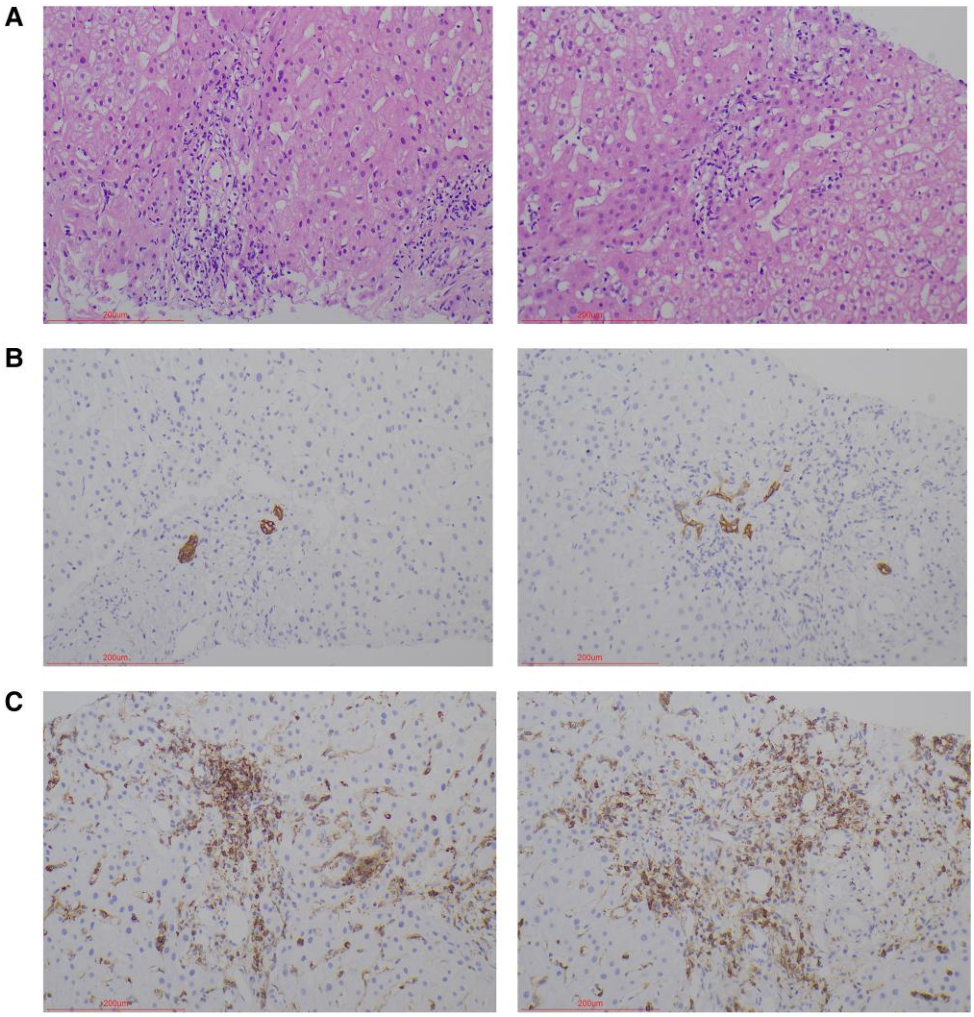

Figure 1. The pathological staging was classified as stage III. (A) Hematoxylin and eosin (HE) staining revealed mild disruption of the lobular architecture with occasional focal necrosis. Slight sinusoidal dilation and mild mononuclear cell infiltration are present. A few portal areas exhibited mild inflammatory infiltration, primarily by mononuclear cells, and mild interface hepatitis. Significant fibrous tissue proliferation was observed in the portal areas, leading to the formation of bridging fibrous septa. (B) Cytokeratin 19 (CK19) staining highlights bile ducts, further confirming the reduction or absence of bile ducts in the portal areas, with some ducts appearing distorted. (C) Leukocyte common antigen (LCA) staining identified lymphocytes, further confirming the extensive lymphocytic infiltration in the portal areas.

ducts in the portal areas, with some ducts appearing distorted. Additionally, leukocyte common antigen staining identified lymphocytes, further confirming extensive lymphocytic infiltration in the portal areas (Fig. 1).

Treatment

Following determination of a diagnosis, the patient was put on ursodeoxycholic acid 15 mg/kg/day and prescribed a dietary management that includes consuming small, frequent, low-carbohydrate meals to provide relief [10].

Outcome and Follow-up

A 3-month follow-up was conducted, which led to the classification of liver function as Child-Pugh grade A (Child 1). During the follow-up, it was observed that liver function had significantly improved. The serum albumin level was 39 g/L (5.66 μmol/L) (normal reference range: 35-50 g/L, 5.08-7.25 μmol/L), alkaline phosphatase was within the normal range, and γ-glutamyl transpeptidase was mildly elevated at 69 U/L. The total bilirubin level was slightly elevated at 22.4 μmol/L (1.31 mg/dL) (normal reference range: 5-21 μmol/L; 0.29-1.23 mg/dL). Continuous glucose monitoring revealed a reduction in the time below range for hypoglycemia, from 2.4% to 0.7%. The patient reported no significant feelings of hunger and maintained consciousness throughout the day without any episodes of loss of consciousness.

Discussion

Hypoglycemia in nondiabetic individuals is a rare metabolic emergency with substantial morbidity and mortality risks. Often overlooked during medical history evaluation, it presents a diagnostic challenge and can be life-threatening if not promptly identified and treated. Patients present with several variable and nonspecific symptoms, including increased adrenergic activity and/or neuroglycopenia [11]. Therefore, the diagnosis of hypoglycemia is complex, requiring adoption of the Whipple triad approach, comprising symptoms consistent with hypoglycemia (eg, shakiness, irritability, confusion, rapid heartbeat, hunger), a concurrent blood glucose level

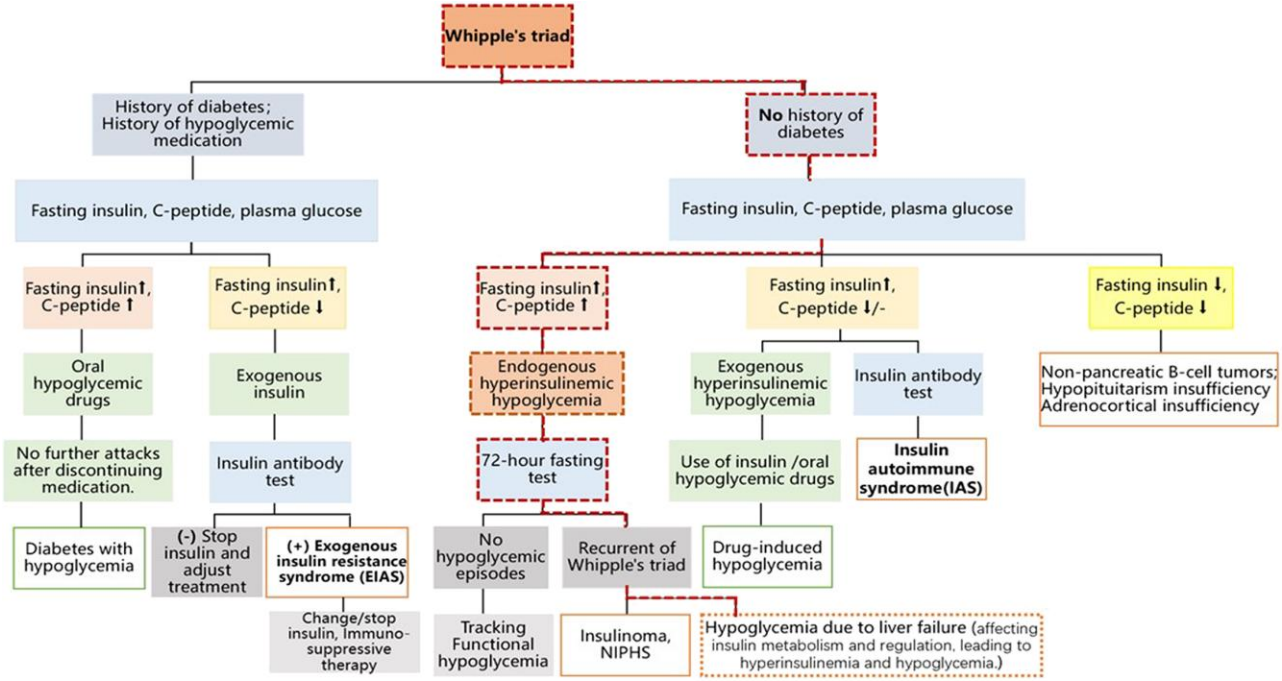

Figure 2. Causes of hypoglycemia. The diagnostic clinical pathway for this patient is depicted by the dotted line.

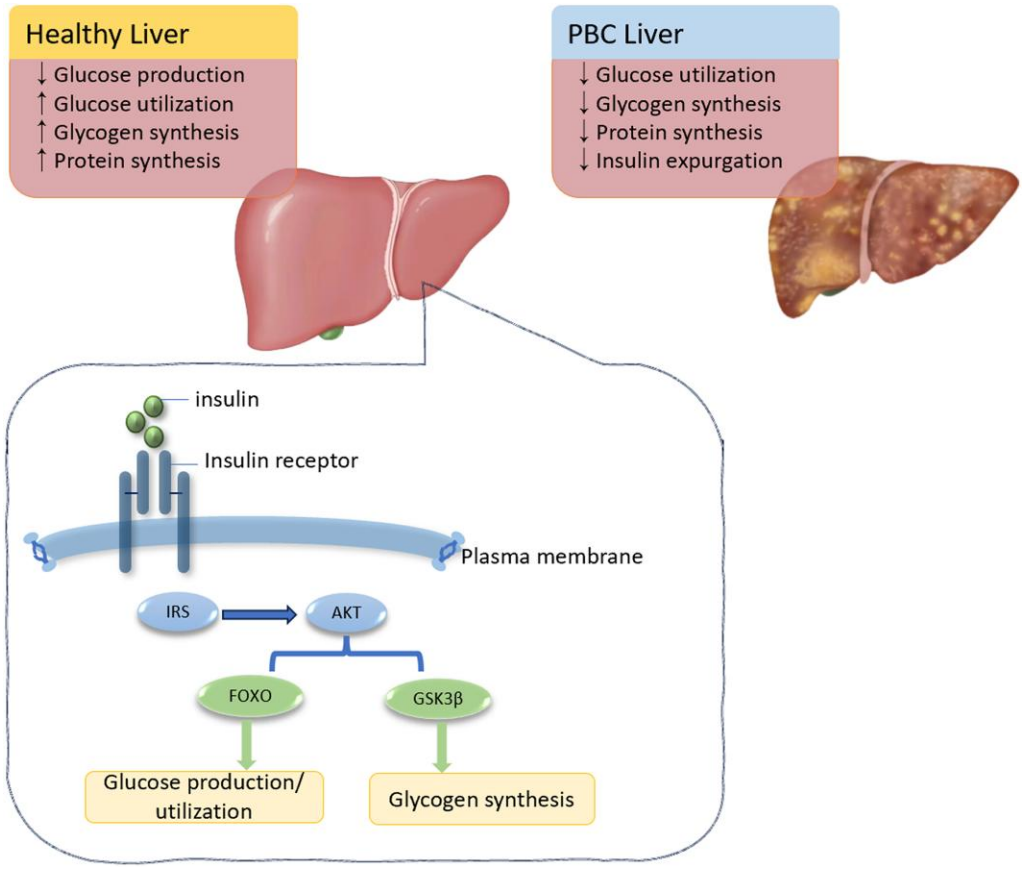

Figure 3. Insulin action in the liver under physiological and pathological conditions. In a healthy liver, insulin binds to the insulin receptor on the plasma membrane, triggering downstream signaling pathways that regulate glucose production, utilization, and glycogen synthesis. However, in the liver affected by primary biliary cholangitis (PBC) and cirrhosis, liver dysfunction can disrupt insulin metabolism and regulation, resulting in hyperinsulinemia and hypoglycemia.

Table 6. Characteristics of reported PBC cases with hypoglycemia

References	Gender	Age	Complications	Type of hypoglycemia	Autoantibodies	Etiology	Treatment
Selinger et al (1987) [5]	F	43	Immune-mediated thrombocytopenic purpura	Hyperinsulinemic hypoglycemia	AMA 1:160 ANA 1:80 Antiplatelet antibodies 25.23 mg IgG per 106 platelets insulin receptor autoantibody 1:100	IAS	Glucocorticoids
van Leeuwen et al (2002) [7]	F	38	Rapid development of jaundice	ND	AMA 1:320 ANA 1:1280 SMA 1:40	Subfulminant hepatic failure secondary to AIH,	Liver transplantation
Bossu Estour et al (2010) [6]	M	68	Noninfiltrating urothelial carcinoma of the bladder; esophageal varices	Hyperinsulinemic hypoglycemia	AMA 1:320 ANA 1:1280	IAS	Glucocorticoids

Abbreviations: AIH, autoimmune hepatitis; AMA, antimitochondrial antibody; ANA, antinuclear antibodies; IAS, insulin autoimmune syndrome; SMA, anti-smooth muscle antibody; ND, no data.

below 2.75 mmol/L (50 mg/dL), and the resolution of symptoms following glucose administration and correction of the hypoglycemic state [8]. Adult individuals without diabetes may develop hypoglycemia because of various factors [12], including primary and secondary adrenal insufficiency, insulinomas, among others [13, 14] (**Fig. 2**).

Recurrent episodes of altered consciousness may stem from diverse causes, such as neurological, cardiovascular, and metabolic conditions [15]. Coma is observed in approximately 25% of severe hypoglycemia cases, a condition defined by the inability of the individual to self-treat [16]. Moreover, hypoglycemia can stimulate sympathetic and adrenal systems, inducing neurophysiological and cerebral blood flow changes, which can potentially induce coma, seizures, hemiplegia, and cognitive dysfunction, especially in young children [17] and the elderly [18]. Hypoglycemia can also affect cardiovascular processes, including blood flow, clotting, etc [19]. Thus, patients experiencing recurrent level 2 or level 3 hypoglycemia require prompt medical intervention, which may involve an adjusted treatment regimen, behavioral interventions, and the incorporation of technology to prevent and identify underlying causes [20, 21].

In this report, the patient presented with central nervous system depression, initially misdiagnosed as epileptic seizures. However, dynamic blood glucose monitoring and hypoglycemia diagnosis revealed fasting hypoglycemia associated with hyperinsulinism, caused by impaired insulin metabolism from liver dysfunction. Although the complexities of insulin metabolism in the liver remain unclear, researchers suggest that insulin binds to receptors on hepatocyte membranes, leading to internalization and degradation of the insulin-receptor complex, which subsequently activates by Forkhead box O and glycogen synthase kinase-3β (GSK3β) signaling [22]. Impaired binding affinity of insulin to its receptors decreases the clearance rate of insulin from the liver, resulting in endogenous hyperinsulinemia (Fig. 3) [23].

Endogenous hyperinsulinemia is marked by plasma concentration of glucose < 3.0 mmol/L (54 mg/dL), with insulin level of ≥ 3.0 μU/mL (18 pmol/L) and C-peptide ≥ 0.6 ng/mL (0.2 nmol/L) [8]. In this case, hyperinsulinemia was due to reduced insulin inactivation caused by liver dysfunction. Besides the diagnostic criteria for hyperinsulinemic hypoglycemia proposed in the 2009 Clinical Practice Guidelines for Adult Hypoglycemia by the Endocrine Society [8], the West China Hospital has adopted additional criteria: named the oral glucose tolerance test index [24]. Moreover, the Peking Union Medical College Hospital has proposed more stringent diagnostic cutoff points for hyperinsulinemic hypoglycemia [25].

Some studies have reported that an insulin/C-peptide molar ratio > 1 indicates endogenous hyperinsulinemia [26]. However, an observation study by Peking Union Medical College showed that the insulin to C-peptide molar ratios were not consistently > 1 in patients with confirmed diagnoses of IAS. Therefore, they suggested that low sensitivity of insulin to C-peptide molar ratio may reflect IAS or even endogenous hyperinsulinemia [27].

Hyperinsulinemic hypoglycemia associated with PBC is rare, with only 3 reported cases. The first, in 1987, involved a 43-year-old Caucasian woman with PBC and IAS [5]. The second, in 2010, described a 68-year-old man with hypoglycemia linked to PBC and positive IAA [6]. A third case involving a 38-year-old African-American woman with PBC who developed hypoglycemia following subfulminant hepatic failure secondary to AIH was reported. However, the etiology of hypoglycemia has not been clarified [7] (**Table 6**). These findings support the association of PBC with autoimmune syndromes. In this case, repeated tests did not identify insulin-related antibodies. Pathological staging revealed hepatocellular and cholestatic injury. After excluding other causes of hyperinsulinemic hypoglycemia, a definitive diagnosis was made, attributing the hypoglycemic episodes to intrinsic insulin metabolism abnormalities caused by PBC-related liver dysfunction.

Learning Points

- This case increases awareness about the possibility of hypoglycemia in patients with atypical central neural system depressive symptoms or seizures.
- Differential diagnosis of hypoglycemia should consider hyperinsulinemic hypoglycemia.
- Besides liver dysfunction, AIH and IAS, autoantibody should be screened if there is abnormal liver function together with hypoglycemia.

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Contributors

All listed authors substantially contributed to the conception and design of the study, data acquisition, analysis, interpretation, drafting, and editing of the manuscript. J.S., J.X., and Y.L. contributed to the diagnosis and management of this patient. Y.C., L.W., and W.C. participated in the designing of the study, data acquisition, analysis, interpretation, drafting, and editing of the case report. All authors reviewed and approved the final draft.

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Disclosures

Ethical approval for this study was obtained from the Ethics Committee of the Eighth Medical Center of PLA General Hospital (No. 309202406063193).

Informed Patient Consent for Publication

Signed informed consent obtained directly from patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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