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Recurrent hypoglycemic coma and diabetic ketoacidosis caused by insulin antibody. A rare case of type 1 diabetes mellitus

YAPING KONG[1,a,*], YAO ZHANG[2,*], LI CHENG[1,b], CONG LING[3], XILING HU[4,c]

ABSTRACT

Insulin antibodies (IAs) induced by exogenous insulin rarely cause hypoglycemia. However, insulin autoantibodies (IAAs) in insulin autoimmune syndrome (IAS) can cause hypoglycemia. The typical manifestations of IAS are fasting or postprandial hypoglycemia, elevated insulin level, decreased C-peptide levels, and positive IAA. We report a 45-year-old male with type 1 diabetes mellitus (T1DM) treated with insulin analogues suffering from recurrent hypoglycemic coma and diabetic ketoacidosis (DKA). His symptoms were caused by exogenous insulin and were similar to IAS. A possible reason was that exogenous insulin induced IA. IA titers were 61.95% (normal: < 5%), and the concentrations of insulin and C-peptide were > 300 mU/L and < 0.02 nmol/L when hypoglycemia occurred. Based on his clinical symptoms and other examinations, he was diagnosed with hyperinsulinemic hypoglycemia caused by IA. His symptoms improved after changing insulin regimens from insulin lispro plus insulin detemir to recombinant human insulin (Gensulin R) and starting prednisone.

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***Key words**: Diabetes Mellitus, Type 1; Diabetic Ketoacidosis; Insulin Antibodies.*

Hipoglicemia hiperinsulinémica causada por anticuerpos antiinsulina. Informe de un caso

Los anticuerpos contra la insulina (AI) inducidos por la insulina exógena raramente causan hipoglucemia. No obstante, los autoanticuerpos contra la insulina (AIA) en el síndrome autoinmune de insulina (SAI) pueden causar hipoglucemia. Las manifestaciones típicas del SAI son la hipoglucemia en ayunas o posprandial, niveles elevados de insulina, la disminución del nivel de péptido C y AIA positivos. Presentamos un paciente hombre de 45 años con diabetes mellitus de tipo 1 (DMT1) tratado con análogos de insulina, que sufría comas hipoglucémicos recurrentes y cetoacidosis diabética (CAD). Sus síntomas fueron causados por la insulina exógena y fueron similares al SAI. La posible razón fue que la insulina exógena indujo AI. El título de AI era del 61,95% (Normal:

[1]School of Nursing, Sun Yat-sen University, No. 74, Zhongshan Er Road, Guangzhou, Guangdong 510085, China.
[2]Department of Endocrinology and Metabolism, The Third Affiliated Hospital of Sun Yat-sen University, No.600 Tianhe Road, Guangzhou, Guangdong, 510630, China.
[3]Department of Neurosurgery,The Third Affiliated Hospital of Sun Yat-sen University, No.600 Tianhe Road, Guangzhou, Guangdong, 510630, China.
[4]Department of Medicine, The Third Affiliated Hospital of Sun Yat-sen University, No.600 Tianhe Road, Guangzhou, Guangdong, 510630, China.
[a]Postgraduate.
[b]Associate Professor.
[c]Associate Senior Nurse.

*These authors contributed equally to the paper.

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Corresponding to:
Xiling Hu, RN.
Department of Medicine, The Third Affiliated Hospital of Sun Yat-sen University, No.600 Tianhe Road, Guangzhou, Guangdong, 510630, China.
flying3061983@163.com

< 5%), y las concentraciones de insulina y péptido C eran > 300 mU/L y < 0,02 nmol/L cuando se producía la hipoglucemia. Basados en sus síntomas clínicos y otros exámenes, se le diagnosticó hipoglucemia hiperinsulinémica causada por la AI. Sus síntomas mejoraron después de cambiar el régimen de insulina de lispro más insulina detemir a insulina humana recombinante (Gensulin R) y de empezar a tomar prednisona.

***Palabras clave**: Anticuerpos Insulínicos; Cetoacidosis Diabética; Diabetes Mellitus Tipo 1.*

Hypoglycemia is a major problem in patients with diabetes mellitus (DM), especially among those with type 1 diabetes mellitus (T1DM) who are dependent on insulin administration. Hypoglycemic coma (HC) and diabetic ketoacidosis (DKA) are severe and potentially life-threatening complications of DM that require prompt recognition, diagnosis, and treatment[1]. There are two kinds of antibodies against insulin, one that involves the autoimmune system (insulin autoantibody: IAA) and the other one associated with exogenous insulin administration (insulin antibody: IA)[2]. IAA is sometimes found in patients with type 1 diabetes mellitus (T1DM) and also in those with insulin autoimmune syndrome (IAS). IAS features recurrent hyperinsulinemic hyperinsulinemia, positive IAA, and treatment without exogenous insulin[1], because of exposure to sulfhydryl-containing drugs, alpha-lipoic acid drugs, and underlying autoimmune diseases[2-4]. Insulin antibodies are often seen in patients undergoing insulin treatment; however, they do not cause hyperglycemia or hypoglycemia[5, 6-8]. It is because these antibodies almost never bind to insulin ("low capacity"), or, if they do bind to insulin, they never separate ("high affinity"), which is contrary to IAA with high capacity and low affinity[7,9]. Here, we report a rare case of T1DM in a patient suffering from recurrent HC and DKA associated with IA, which was related to the long-term use of exogenous insulin analogues, and had clinical manifestations similar to IAS.

Case presentation

A 45-year-old man was diagnosed with T1DM 15 years ago and was treated with multiple-dose insulin injection for 10 years. Initially, he received porcine insulin for 2 years and then Humulin R and Humulin N injection. About 5 years ago, his insulin was changed from human insulin to analog insulin-insulin lispro plus insulin detemir. In the past 4 years, both HC and DKA events have repeatedly occurred alternately. Severe HC mostly occurred during midnight or early morning with blood glucose levels at 1-2 mmol/L and was very difficult to correct. The symptoms of DKA included nausea, vomiting large amounts of stomach contents, abdominal pain, weakness, and confusion. Therefore, he was admitted to the emergency department of the local hospital and hospitalized many times. At first, HC and DKA happened about 4-5 times annually, but the frequency increased to more than 10 times in the past year. The patient was taken to the emergency department of the local hospital by ambulance, because his blood sugar levels were below 2 mmol/L, 2 days before. His consciousness and blood glucose level recovered after being administrated intravenous injection of 40 g glucose; however, after half an hour, his hypoglycemia recurred with no awareness. Insulin was discontinued, and he was referred to our hospital for further treatment and understanding of the etiology of recurrent HC and DKA.

On admission, his height was 172 cm and weight was 67 kg (BMI: 22.64 kg/m^2). His insulin was stopped for 6 h. His blood glucose and blood ketone values were 33.1 mmol/L and 3.7 mmol/L, respectively. His serum HCO_3^- was 17 mmol/L and pH was 7.3 mmol/L. His glycosylated hemoglobin (HbA1c) was 9.5% and his renal and liver function tests were normal. He denied an exposure history to sulfhydryl drugs and DL-thioctic acid. He had no family history of diabetes and no personal or family history of thyroid disease, cancer, or other autoimmune diseases. During hospitalization, the DKA and HC recurred with irregular patterns. However, his hypoglycemia often occurred at

Table 1. Blood glucose level and related value of insulin, C-peptide, IA binding rate

Parameter	12-17 2:30	12-19 6:30	12-22 19:33	12-25 15:44	12-27 0:50	unit	Normal range
Blood glucose	1.19	9.8	19.31	19.66	4.51	mmol/L	3.9-6.1
insulin	> 300	28.67	8.61	32.35	53.23	mu/L	3-25
C- peptide	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	nmol/L	0.27-1.28
Binding rate of IA	61.95	52.51	55.48	/	52.05	%	< 5

night or before meals. Hypoglycemia fluctuated in the range of 1.19-3.9 mmol/L, and hyperglycemia fluctuated in the range of 16.7-33.1 mmol/L, but blood glucose could not be detected when it was too high or too low (Figure 1). We administered intravenous fluids and insulin to correct the DKA and intravenous to correct HC. We used a continuous glucose monitoring system (Medtronic 722) to monitor the patient's blood glucose fluctuations and Medtronic 722 insulin pump (insulin aspart) to regulate his blood glucose. We modified his insulin dose very carefully.

The patient had normal thyroid function, with free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels being 3.61 pmol/L, 20.69 pmol/L, and 2.799 IU/mL, respectively. He was also examined for adrenal function, with plasma cortisol levels of 544.150 nmol/L at 08:00 h, 304.350 nmol/L at 16:00 h, and 102.340 nmol/L at 24:00 h. Abdominal contrast-enhanced computed tomography (CT) revealed no lesions in the pancreas and upper abdomen. We tested his insulin, C-peptide, and insulin antibody binding rate levels when HC and DKA occurred (Table 1). We found that when he suffered from hypoglycemia, his insulin level and IA binding rate was high, but C-peptide was never detected, and when he suffered from hyperglycemia, his insulin level and IA binding rate was decreased.

We changed the analog insulin aspart to recombinant human insulin (Gensulin R) in the insulin pump, but he developed hypoglycemia and hyperglycemia twice in the same night. A week later, steroid treatment was initiated by oral administration of prednisolone (10 mg/t.i.d.). After taking steroids for a week, the frequency of his hypoglycemic episodes was markedly reduced to approximately once a weekend and then to none. His insulin regimen comprised multiple dose injections of Humulin R and Humulin N at the time of discharge. He was then discharged uneventfully with 30 mg oral prednisolone per day.

Discussion

Insulin antibodies with low volume and high affinity rarely cause hypoglycemia or hyperglycemia in patients receiving insulin therapy[8]. The biochemical and clinical characteristics of IA are similar to IAA. IAA produced by patients with IAS is characterized by high volume and low affinity, which may lead to the appearance of blood glucose instability in patients[6]. Since he changed his insulin from recombinant human insulin to analog insulin lispro and detemir 5 years ago and then suffered from recurrent hypoglycemia and DKA. His symptoms improved after the insulin analogue was replaced with recombinant human insulin (Gensulin R) using glucocorticoids. There were no symptoms of hypoglycemia, and IA test showed negative results. Therefore, IA induced by exogenous insulin was probably the cause.

The IAs likely combined with exogenous insulin, which induced immunological insulin resistance and led to a higher postprandial peak in blood glucose. However, this combination was reversible: when bound insulin dissociated due to the change in pH at night, free insulin increased, thereby resulting in hypoglycemia[10-12]. Mostly, the hypoglycemic episodes happened during early morning and the late postprandial period, and it was assumed that most insulin secreted through endogenous origin or administered via exogenous methods was bound to antibodies

and then dissolved from the complex to exert its effect, thus producing severe hypoglycemia[13-14]. Some unknown factors may have promoted the sudden dissociation of antigens and antibodies, and patients sometimes experience hypoglycemia without obvious inducement. IAs have a long half-life in the body. A small prospective research study reported that while IA levels gradually decrease within 1 month after insulin withdrawal, the full disappearance of IAs can take more than 1-2 years[10,15].

For most patients with IAS, the symptoms would be relieved quickly after stopping insulin medication. However, our patient with T1DM was dependent on insulin treatment, and when he suffered from HC, most physicians tended to reduce or stop insulin for a while[8,9,15-19], which then led to hyperglycemia and DKA. This cycle of HC alternating with DKA happened many times, but was concealed behind the T1DM characteristic of irregular blood glucose levels. However, when he suffered from severe hypoglycemia (1.9 mmol/L), his plasma insulin became extremely high (>300) with undetected C-peptide and high binding rate of IA (61.95%). When he suffered from hyperglycemia (19.66 mmol/L), his insulin level (8.62 mu/L) and IA binding rate (52.05%) were decreased. He took 30 mg prednisone tablets daily and his condition was relieved. We speculated that a mechanism similar to IAA must have occurred in his body since his symptoms was similar to IAS,and IAs were formed through an immune reaction against exogenous insulin in his body[16].

Nevertheless, the triggering factors that cause the dissociation of insulin and insulin antibodies are still not clear. The reasons for IA induction are heterogeneous and remain incompletely understood. Insulin antibodies have emerged from insulin analogs with high capacity and low affinity and should be proven by characterizing these different clones of antibodies. Through the case presented here, we wish to highlight the possibility that IA induced by exogenous insulin analogs may have similar clinical characteristics as insulin autoantibodies (IAA) seen in IAS and should be considered in diabetic patients treated with insulin. IA induced by exogenous insulin analog should be one of the differential diagnosis for patients having T1DM with frequent hyperinsulinemic hypoglycemia.

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