Yonsei Medical Journal
Vol. 45, No. 1, pp. 140 - 144, 2004

Case Report

A Case of Autoimmune Hypoglycemia Complicated with Diabetic Ketoacidosis

Myoung Sook Shim[1], Moon Young Kim[1], Mi Jin Kim[2], Yeon Lee[1], Byung Jun Lee[1], Choon Hee Chung[1], and Young Goo Shin[1]

[1]Division of Endocrinology, Wonju College of Medicine, Yonsei University, Wonju, Korea;
[2]Division of Internal Medicine, College of Medicine, Konkuk University, Seoul, Korea.

Autoimmune hypoglycemia is characterized by hyperinsulinemia, fasting hypoglycemia, and the presence of insulin auto-antibodies without previous exposure to exogenous insulin. We experienced a case of autoimmune hypoglycemia without diabetes mellitus or any evidence of insulinoma. The insulin auto-antibody and insulin receptor auto-antibody were present. We diagnosed the patient as having autoimmune hypoglycemia and treated with glucocorticoid. After treatment, the hypoglycemic symptoms were resolved. However, four months later, the patient was readmitted with transient diabetic ketoacidosis. After recovery, he showed no signs of diabetes mellitus. We believe that insulin auto-antibodies may play a role in autoimmune hypoglycemia and diabetic ketoacidosis, but its role and mechanism are not precisely known. Further studies are needed to define the action mechanisms and the functions of insulin auto-antibodies: here we present case with a relevant literature.

Key Words: Autoimmune hypoglycemia, insulin auto-antibody, Insulin receptor auto- antibody, diabetic ketoacidosis

INTRODUCTION

Autoimmune hypoglycemia is a disease that is developed by auto-antibodies of insulin and insulin receptors.[1] Although the cause of the auto-antibody formation without a history of medication for diabetes mellitus is not clear, it is known to be related with autoimmune disease or with medications that include the sulfhydryl group.[2-4] Diabetic ketoacidosis develops during insulin deficiency in diabetics and is one of the most important and severe complications of the disease, especially in type I diabetes mellitus patients. Autoimmune hypoglycemia and diabetic ketoacidosis have an opposing relationship in terms of the disease entity. We experienced the first case of diabetic ketoacidosis with autoimmune hypoglycemia without a history of diabetic mellitus, and we present the case with a review of the literature.

Received February 4, 2003
Accepted July 30, 2003

Reprint address: requests to Dr. Young Goo Shin, Division of Endocrinology, Wonju College of Medicine, Yonsei University, Ilsan-dong, Wonju 220-701, Korea. Tel: 82-33-741-1247, Fax: 82-33-731-5338, E-mail: sygm@wonju.yonsei.ac.kr

CASE REPORT

First admission

A 47-year-old man exhibited symptoms of repeated unconsciousness at dawn for 3 days before he visited a clinic. Upon signs of hypoglycemia, he was injected with dextrose solution and transferred to our hospital. On arrival, his blood sugar level was 31 mg/dL. He had been diagnosed with tuberculous pleuritis 3 years ago and had received medication for 6 months. There was no other definite medication history. Despite stable vital signs, he was unconscious and appeared acutely ill, but promptly recovered after an injection of dextrose solution. There were no abnormal pigmentations or hypertrophy on the occipital and axillary areas or any other abnormalities. On admission, no abnormal findings were found in complete blood cell counts, urinalysis, serum electrolytes, renal function, or liver function. Thyroid function studies showed no abnormalities and thyroid auto-antibody was within the normal ranges. At the time of hypogly-

cemic attack, blood insulin and c-peptide levels were 8.49 μIU/mL and 4.01 ng/mL (0.4-4.0 ng/ml), respectively, and hypoglycemia developed at 6 hours in the 72-hour fasting test, with glucose and insulin levels at 23 mg/dL and 8.20 μIU/mL, respectively. To rule out diabetes mellitus, we performed the oral glucose tolerance test, which did not indicate the disease (Table 1). We also performed magnetic resonance imaging (MRI) of the pancreas to rule out insulinoma, but no abnormal mass was evident and transhepatic portal and splenic venous sampling showed no region with abnormally elevated insulin or c-peptide levels (Fig. 1 and 2, Table 2). The 72-hour fasting test revealed ACTH 46.51 pg/mL, cortisol 11.43 μg/dL, growth hormone 4.21 ng/mL, glucagon 58.9 pg/mL (40 - 130 pg/mL), norepinephrine 6.6 pg/mL (supine 70 - 750 pg/mL and standing 200 - 1700 pg/mL), and epinephrine 5.8 pg/mL (supine 0 - 110 pg/mL and standing 0 - 140 pg/mL) when hypoglycemic symptoms developed. These results were lower than expected; therefore, we performed a combined pituitary function test, which showed depressed growth hormone (ACTH) and FSH levels (Table 3). Suspecting partial hypopituitarism, a sellar MRI scan was performed, revealing pituitary microadenoma. Antigastric parietal cell antibody, antiadrenal cortex antibody, and antipituitary antibody were all negative. Insulin auto-antibody was positive (97.5%) and insulin receptor auto-antibody was also positive. Therefore, the patient was diagnosed as having autoimmune hypoglycemia and was medicated with 30 mg of oral prednisone per day. After the start of the medication, the hypoglycemic attack at dawn disappeared, and we gradually decreased the dose of oral prednisone. Subsequently, the insulin auto-antibody level concomitantly decreased by 90%.

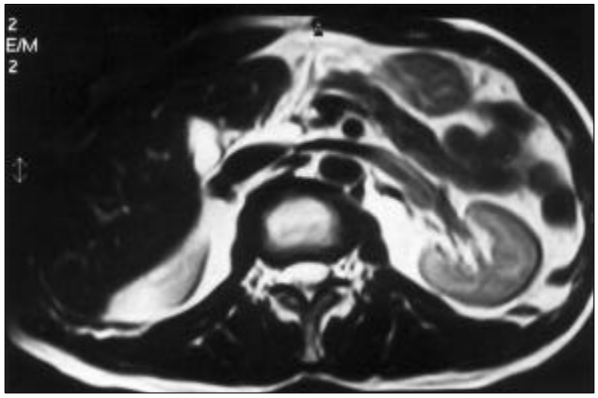

Fig. 1. Pancreas MRI scan shows no evidence of pancreatic mass.

Second admission

After we reduced oral prednisone to 5 mg per day, the patient discontinued the medication by himself. Four months after admission, he was readmitted to the medical intensive care unit due to diabetic ketoacidosis with repeated nausea and vomiting following 7 days of common cold symptoms. On admission, the patient was alert with stable vital signs and there were no abnormal findings, except mild peripheral pitting edema on physical examination. The white blood cell count showed leukocytosis at 21,420/mm^3, while renal and liver function studies and serum electrolyte levels were normal. His blood glucose

Table 1. 75g Oral Glucose Tolerance Test during the 1st Admission Due to Hypoglycemic Attack

Time(min)	Basal	30	60	90	120
Glucose(mg/dL)	23	140	175	128	136
Insulin(μIU/mL)	9.82	9.95	11.63	12.38	11.02
C-peptide(ng/mL) (0.4-4.0ng/mL)	0.64	0.65	0.76	0.8	0.72

Table 2. Insulin and c-peptide Levels During the Transportal and Splenic Venous Sampling

	Portal vein	5 cm	4 cm	3 cm	2 cm	1 cm	Splenic vein
Insulin(μIU/mL)	16.93	20.31	19.98	20.29	21.01	20.76	20.07
C-peptide(ng/mL)	9.96	14.17	13.92	9.79	6.88	5.96	6.05

level was 592 mg/dL, and urinalysis showed a urine specific gravity of 1.025, pH 5.0, and glucose and ketone levels of 4+ and 2+, respectively. Arterial blood gas analysis showed a pH of 7.140, PCO_2 15.2 mmHg, HCO_3^- 5.2 mmol/L, and an anion gap 20 mmol/L. After insulin and fluid therapy, the acidosis improved and the sugar level decreased, prompting us to discontinue insulin therapy on the 6th hospital day. On the 7 th day, a hypoglycemic attack occurred (blood sugar 42 mg/dL), and the patient was re-medicated with 60 mg of oral prednisone per day. Because there was no further recurrence of his hypoglycemic symptoms, the medication was discontinued after serially decrementing the dosage. Hypoglycemia did not recur, and after recovery, no evidence of diabetes mellitus has been observed (Table 4).

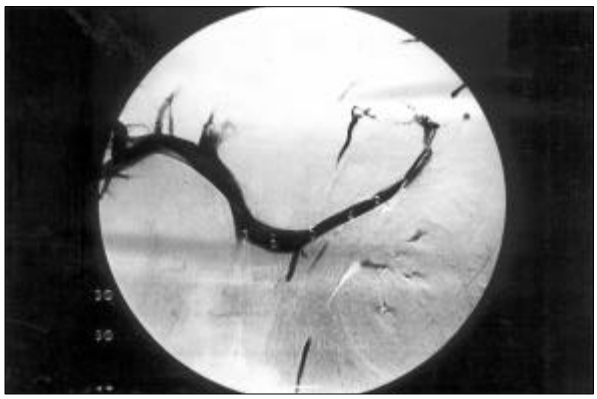

Fig. 2. Transhepatic portal splenic venous sampling. The blood samples were drawn from splenic vein to portal vein with 1 cm intervals for checking of the insulin level. There is no region representing an abnormally elevated step up of insulin or c-peptide level.

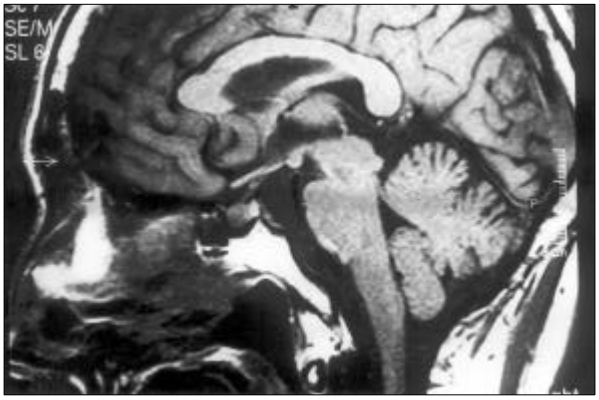

Fig. 3. Sellar MRI scan shows about a 5 mm microadenoma with low signal density in the anterior pituitary gland.

Table 3. The Results of Combined Pituitary Function Test

Time (min)	0	30	60	90	120
Glucose (mg/dL)	83	49	303	77	45
GH (ng/mL)	<0.04	0.14	0.09	0.07	0.26
ACTH (pg/mL)	<1.0	3.2	2.64	<1.0	3.57
Cortisol (μg/dL)	7.22	8.21	6.12	5.08	5.36
FSH (mIU/mL)	3.08	5.03	5.65	5.64	5.45
LH (mIU/mL)	3.27	21.63	21.49	17.27	14.55
TSH (μIU/mL)	1.72	10.63	4.9	5.01	3.42
Prolactin (ng/mL)	5.1	34.86	22.16	11.36	8.61
Epinephrine	125.1 pg/mL		Norepinephrine	551.0 pg/mL	
T3	1.22 ng/mL		free T4	1.31 ng/mL	
E2	< 10 pg/mL		Testosterone	4.9 ng/mL	

Table 4. 75g Oral Glucose Tolerance Test During the 2nd Admission Due to Diabetic Ketoacidosis

	Basal	30 min	60 min	90 min	120 min
Glucose(mg/dL)	26	58	77	137	128
Insulin(μIU/mL)	5.53	4.6	6.27	4.38	4.7
C-peptide(ng/mL)	4.36	5.57	6.69	9.73	7.95

DISCUSSION

Hypoglycemia combined with hyperinsulinemia is known to be caused by auto-antibodies acting against insulin and insulin receptors or by postreceptor defects.[1,5] Since Hirata et al.[6] Reported hypoglycemia caused by insulin auto-antibody, which was not associated with previous insulin therapy, the autoimmune hypoglycemia has drawn clinical attention. The diagnosis of autoimmune hypoglycemia can be made based on the presence of insulin auto-antibody, hyperinsulinemia, and fasting hypoglycemia. In our case, the patient had recurrent fasting hypoglycemic symptoms - sweating, drowsiness, and syncope - at dawn for several days with hyperinsulinemia. Therefore, we examined the pancreas by MRI and performed transportal and splenic venous sampling to exclude insulinoma and extrapancreatic insulin-producing tumor and found no evidence of abnormalities (Fig. 1 and 2, Table 2). However, insulin auto-antibody and insulin receptor auto-antibody were positive, so we were able to diagnose the patient as having autoimmune hypoglycemia.

The auto-antibodies related to autoimmune hypoglycemia are the insulin auto-antibody and the insulin receptor auto-antibody, but the mechanism of their formation is unclear. Hirata et al.[2] and Betterle et al.[4] presented cases of Grave's disease and organ-specific autoimmunity, respectively, in the presence of insulin auto-antibody, asserting their relationship with the autoimmune diseases. Also, several groups have reported that a number of drugs that contain the sulfhydryl group (S-H) interact with the disulfide bond of insulin to form haptene, or otherwise they disrupt this disulfide bond and cause an autoimmune reaction, resulting in the formation of insulin auto-antibodies.[3,7-9]

The mechanism of action of these auto-antibodies is not clear, either. Ohneda et al.[10] reported a case of pancreatic islet cell hypertrophy in an autoimmune hypoglycemic patient, indicating that the combination of insulin auto-antibody and insulin should result in a reduction of blood insulin levels, and hence induce the stimulation of islet cells and islet cell hypertrophy, with subsequent increases in the insulin levels of the blood. Folling et al.[11] and Ichihara et al.[8] explained that the increased level of blood immunoreactive insulin, which occurs when a dextrose solution is injected, and the onset of glucose tolerance (by the oral glucose tolerance test) of autoimmune hypoglycemic patients, show that the sugar elevation (with dextrose solution or diet) stimulates the islet cells in the pancreas to secrete insulin. Therefore, secreted insulin molecules bind to the insulin auto-antibody and become inactivated, which results in glucose tolerance. Moreover, the increased sugar level stimulates insulin secretion continuously and forms a large insulin pool. Insulin and insulin auto-antibody dissociates in a certain environment, and if this dissociation occurs in a fasting state, hypoglycemia could develop. Also, as for this mutual relation of auto-antibodies, Elias et al.[12] reported that these have an idiotypic relationship and can form an anti-idiotypic network. In other words, if one of the auto-antibodies is formed first, it could result in hypoglycemia or the resolution of the disease; anti-idiotypic antibodies might be induced. In our case, insulin auto-antibody and insulin receptor auto-antibody were simultaneous, and it was unclear which of them was responsible for the development of hypoglycemia.

In our case, the patient did not have a history of diabetes mellitus, and showed no evidence of any abnormalities on the oral glucose tolerance test. At the time of the second admission, the patient showed definite diabetic ketoacidosis. Re-examination of the oral glucose tolerance test after recovery also showed normal findings. To the best of our knowledge, no reports on autoimmune hypoglycemia have demonstrated the to be associationed with diabetic ketoacidosis. It is also questionable whether a diabetic ketoacidosis can be developed in non-diabetics. Reviewing the literature convinced us that the insulin auto-antibodies combine with insulin and inhibit the action of the insulin, resulting in a relative insulin deficit and an increased secretion of insulin in the islet cells. Furthermore, on dissociation of the insulin and insulin auto-antibody complex, the increased blood insulin level develops hypoglycemia with a mild decrease of the c-peptide level. We also believe that diabetic ketoacidosis results from a relative insulin deficiency, which is developed by

the blocking of insulin action or of insulin receptors by the insulin receptor auto-antibody. This antibody is induced by an anti-idiotypic network of insulin auto-antibodies, or by an increased stability of the insulin and insulin auto-antibody complex, which inhibits dissociation. In this state, the c-peptide secretion may be increased. However, further studies should be undertaken to define the mechanisms and functions of these phenomena.

In general, a fasting hypoglycemia is compensated for by several counter-regulatory hormone systems: glucagon, catecholamine, growth hormone, and cortisol, which prevent severe hypoglycemia in a normal person.[13] Klioua et al.[14] reported that a secretional dysfunction of ACTH, in a pituitary disease, induced a lower response to cortisol and epinephrine under hypoglycemic conditions, which easily lead to an onset of hypoglycemia. In our case, decreased responses in counter-regulatory systems were seen during the 72-hour fasting test, and these observations led us to perform a combined pituitary function test. Partial hypopituitarism with decreased ACTH and GH responses was noted, and we believe this might have contributed to the development of hypoglycemia to some degree. In addition, the microadenoma on the sellar MRI might have either been a non-functioning tumor or partial hypopituitarism.

The clinical course of autoimmune hypoglycemia is generally known to be self-limited, that is, the symptoms are resolved after several weeks or months without management. However, the auto-antibodies may persist for several years. In line with the previous report by Komatsu et al.[15] after administration of glucocorticoid, our patient experienced no recurrence of hypoglycemic symptoms with a decrease of the auto-antibody titer.

REFERENCES

1. Flier JS, Bar Muggio M, Kahn CR, Roth J, Gorden P. The evolving clinical course of patients with insulin receptor auto-antibodies; spontaneous remission or receptor proliferation with hypoglycemia. J Clin Endocrinol Metab 1978;47:985-95.
2. Hirata Y, Tominaga M, Ito JI, Noguchi A. Spontaneous hypoglycemia with insulin autoimmunity in Graves' disease. Ann Intern Med 1974;81:214-8.
3. Hirata Y, Takayama S, Saito M. Fifty patients with "autoimmune" insulin hypoglycemia in Japan. Diabetes 1982;31:154A.
4. Betterle C, Presotto F, Pedini B, Moro L, Slack RS, Zanette F, et al. Islet cell and insulin auto-antibodies in organ-specific autoimmune patients. Their behavior and predictive value for the development of Type 1 (insulin-dependent) diabetes mellitus. A 10-years follow-up study. Diabetologia 1987;30:292-7.
5. Bar RS, Muggio M, Roth J, Kahn CR, Havrankova J, Imperato-Mcginley J. Insulin resistance, acanthosis nigricans and normal insulin receptor in a young woman; evidence for a postreceptor defect. J Clin Endocrinol Metab 1978;47:620-5.
6. Hirata Y, Ishizu H, Ouchi N, Motomura S, Abe M, Hara Y, et al. Insulin autoimmunity in a case with spontaneous hypoglycemia. Jap J Diabetes 1970;13:312-9. (in Japanese).
7. Hirata Y. Methimazole and insulin autoimmune syndrome with hypoglycemia. Lancet 1983;2:1037-8.
8. Ichihara K, Shima K, Saito Y, Nonaka K, Tarui S, Nishikara M. Mechanism of hypoglycemia observed in a patient with insulin autoimmune syndrome. Diabetes 1977;26:5 500-6.
9. Benson EA, Ho P, Wang C, Wu PC, Fredlund PN, Yueng RTT. Insulin autoimmunity as a case of hypoglycemia. Arch Intern Med 1984;144:2351-4.
10. Ohneda A. Hypoglycemia due to apparent autoantibody to insulin. Diabetes 1974;23:41-50.
11. Folling I, Norman N. Hyperglycemia, hypoglycemia attacks, and production of anti-insulin antibodies without previous known immunization. Diabetes 1972;21: 814-26.
12. Elias D, Cohen IR, Shechter Y, Spirer Z, Golander A. Antibodies to insulin receptor followed by anti-idiotype; antibodies to insulin in child with hypoglycemia. Diabetes 1987;36:348-54.
13. Boyle PJ, Cryer PE. Growth hormone, cortisol, or both are involved in defense against, but are not critical to recovery from, hypoglycemia. Am J Physiol 1991;260: E395-E402.
14. Klioua N, Ruget G, Selz F, Cuche J-L, Benmiloud M. Plasma catecholamines after insulin hypoglycemia in Sheehan's syndrome. J Clin Edocrinol Metab 1987;64: 1323-7.
15. Komatsu M, Aizawa T, Shinoda T, Yamada T, Mochizuki T. Case report; ACTH deficiency and TSH hypersecretion in a patient with empty sella turcica. Am J Med Sci 1989;297:186-9.