Turkish Journal of Endocrinology and Metabolism, (2000) 4 : 147-150 **CASE REPORT**

Severe Insulin Resistance Syndrome with Spontaneous Remission - Case Report

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There are some rare but severe insulin resistance disord ers with severe target cell resistance to insulin. In this article, we describe an unusual case of severe insulin resistance syndrome with spontaneous remission periods. A 34-year-old male patient with Type 2 for 13 years was admitted to the inpatient clinic because of very high blood glucose levels. Although his diabetes mellitus insulin dose was increased to 260 U/day administered with four daily insulin injections, his blood glucose levels did not respond. In a steady state of treatment his blood glucose levels suddenly decreased to hypoglycemic levels and his insulin requirement ceased. After 14 months of follow-up in euglycemic status without insulin therapy, hyperglycemic symptoms recurred. Hyperglycemic and euglycemic episodes recurred again twice with shorter euglycemic periods. Insulin receptor antibody was detected. These findings are consistent with autoimmune severe insulin resistance syndrome type B with spontaneous remission.

Key words : Insulin resistance, autoimmunity, type B

Introduction

Insulin resistance is defined as a subnormal biological response to a given concentration of insulin. It has been determined that the average rate of endogenous insulin secretion in normal adults is 20-60 units per day. Requirement of more than 100 units (1.5 U/kg) of exogenous insulin to achieve euglycemia in an insulin treated diabetic patient is accepted as insulin resistance (1-3).

There are many clinical settings such as type 2 diabetes mellitus, obesity, pregnancy, Cushing's Syndrome and acromegaly which can cause mild insulin resistance (3,4). In these clinical conditions insulin resistance plays an important role in the course of the disorder. Other than these mild insulin resistance situations there are some rare but severe insulin resistance disorders with extreme hyperinsulinemia and severe target cell resistance to insulin. These are called severe insulin resistance syndromes (1,5-8). In this article, we describe an unusual case of severe insulin resistance syndrome with spontaneous remission periods.

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Case report

A 34-year-old obese (BMI: 42) male patient with diabetes mellitus was admitted to the inpatient clinic because of very high blood glucose levels. He had been diabetic since he was years old and hypertensive since he was 29 years old. When diabetes mellitus was first identified he had been advised to take oral hypoglycemic pills (sulfonylurea) for 2 years and then had begun to receive insulin therapy with dosages between 60-90 units/day. He had kept outpatient follow-up irregularly,

and because of rare hypoglycemic reactions he had partly abandoned insulin administrations. Blood pressure had kept under control with trandolapril in doses of 2 mg/day. He had been investigated for secondary causes of obesity, but no underlying cause had been found. He had had a diagnosis of psychosis and had been treated with major tranquilizers for 3 years.

At admission he was suffering from weakness, insomnia and hallucinations. Blood pressure was 160/90 mmHg. He was 148 kg in weight and 185 cm in height (BMI=42). Waist to hip ratio was 1.02. Physical examination did not reveal any abnormal findings. Blood cell counts, urine examinations (except glucosuria), serum electrolyte levels and hepatic enzyme investigations were within normal ranges. Blood glucose level was 23 mmol/L, hemoglobin A1c 12.7%, triglyceride level was 2.72 mmol/L, total cholesterol level was 6.34 mmol/L and HDL-cholesterol level was 0.91 mmol/L. Serum insulin level was 452 pmol/L (without insulin injection for about 24 hours), and C-peptide level was 9.6 mg/L. Total and free thyroxine and triiodothyronine levels, morning cortisol level and growth hormone level were within normal ranges in baseline conditions. Dynamic tests for cortisol and growth hormone did not raise any doubts about over production. Cranial imaging by computed tomography displayed no abnormality.

He was given 1200 kcal/day low calorie diet therapy, intensive insulin therapy with 4 injectins a day, trandolapril (2 mg/day), haloperidol (10 mg/day) and biperidine (4 mg/day). Insulin dosage was gradually increased to 260 U/day during the following days of observation but glucose levels remained at 5.6-13.8 mmol/L. Because of the possibility of hallucinations and suicide commitment hypoglycemia was avoided. After 3 weeks of hospitalization, while in a steady state of the therapy his blood glucose suddenly decreased to hypoglycemic levels. Insulin dosage was lowered rapidly but low blood glucose levels recurred. Even though insulin administration was stopped blood glucose levels were within normal rangs. Fasting glucose levels were between 3.5-6.1 mmol/L and postprandial levels were between 7.2-8.9 mmol/L. An oral glucose challenge test was performed 7 days after cancelling the insulin therapy, which showed only an impaired glucose tolerance curve with a blood glucose level of 8.77 mmol/L at the 2nd hour.

The patient was accepted as suffering from a syndrome of severe insulin resistance and he was examined for concomitants of other autoimmune disorders. He negated having artralgie, rash, photosensitivity, edema, etc. Erythrocyte sedimentation rate and gamma proportion in protein electrophoresis were within normal ranges. Insulin antibodies were not positive. Antinuclear, anti n-DNA, antimitochondrial, anti-smooth muscle and islet cell antibodies were not found. We did not have the opportunity to evaluate antiinsulin receptor antibody He was kept at the inpatient clinic for one more week without insulin injcections. His pre-prandial and 2 hours post-prandial glucose levels were all within normal ranges. He remained in outpatient follow-up without insulin injections for 14 months and had normal glucose levels.

His hyperglycemic symptoms recurred after 14 months of outpatient follow-up without insulin therapy. Insulin treatment was increased to 400 units a day, but blood glucose levels could not be lowered to less than 12 mmol/L. After 5 months of follow-up once again he showed euglycemic period without insulin therapy which lasted only 2 weeks. After 13 months such a period recurred once more making it necessary to lower insulin doses to 20 units a da for only 2 days. Then, he was kept on 640 units insulin therapy with glucose levels between 11.5-19.4 mmol/L. Insulin receptor antibody was weakly positive in a 6.5% (normal range up to 6%) with the radioimmune assay method. Antibody for insulin was not detected. We added 120 mg/day prednisolone for 4 weeks but did not achieve any noticeable improvement. So prednisolone therapy was tapered and then discontinued. He did not accept treatment with cyclophosphamide or plasmapheresis and was discharged on insulin therapy with a 560 units/day dose.

Discussion

Many clinical features of the patient resemble insulin resistance due to anti-insulin antibodies developed by insulin therapy. We know that for many years he had used pork insulin, and also he was a patient who was usually out of regular control. He had a history of having stopped insulin injection several times. He needed 260 units of insulin per day, even though his blood sugar was away from euglycemic levels. But suddenly he

showed hypoglycemic reactions and his insulin requirement began to decrease. High levels of anti-insulin antibodies can serve as an insulin resorvoir and cause hypoglycemia but this effect is temporary. One week later, after cessation of insulin therapy, his blood insulin levels were still very high and his oral glucose tolerance test showed only an impaired glucose tolerance curve. He did not need insulin therapy for 14 months. These findings are not consistent with insulin resistance syndrome due to insulin antibodies. His serum anti-insulin antibody titer also was not found elevated. He lost only 5% of his total body weight and there was no obvious change in his metabolic, physiological or infectious status.

Insulin resistance due to autoantibodies to the insulin receptor is referred to as the Type B severe insulin resistance syndrome (1,2,5) (Tablo 1). Insulin resistance is caused by polyclonal autoantibodies that bind to insulin receptors at or near to the insulin binding site, thereby impairing their function (9-12). As in other autoimmune disorders, the type B syndrome arises from a defect in the regulation of the immune system rather than from an abnormality of the tissue receptors (13,14). Most of them need very high levels of exogenous insulin therapy (15,16). As with other autoimmune disorders, waxing and waning of symptoms over time is frequently observed, and some of these patients have experienced a spontaneous remission of their hyperinsulinemia (9,10,13).

Table 1. Classification of severe insulin resistance syndromes.

Genetic defects in insulin receptor
Type A syndrome
Rabson-Mendel Syndrome
Leprechaunism
Immunologic, autoimmune
Antibodies to the insulin receptor
Type B syndrome
Ataxia telengiectasia
Antibodies to insulin
Disorders of unknown etiology
Congenital
Dominant inhertitance (Köbberling-Dunnigan syndrome)
Autosomal recessive inheritance (Seip syndrome)
Acquired
Generalized (Lawrence syndrome)
Partial lipotrophy

Many of the clinical characteristics of our patient are consistent with type B syndrome. He needed more than 640 units (4.48 U/kg) of insulin, he showed euglycemic episodes without insulin therapy and insulin receptor antibodies were detected. Contrary to what is commonly seen in patients with insulin receptor antibodies, our patient was not female, and did not have any sign of hyperpigmentation. Acantosis nigricans nearly always develops in these patients and these patients also have symptoms or laboratory test results of other autoimmune diseases (3,12,17), which are lacking in our patient.

Spontaneous remission of insulin resistance with disappearance of insulin receptor antibodies has been documented (1,13). Our patient also had episodes of spontaneous remission but we did not have the possibility to show an antiboty titer. These episodes became shorter and we demonstrated insulin receptor antibody in the last hyperglycemic period. There are many treatment regimens reported to be effective (3, 16). Magsino et al. reported a patient with severe insulin resistance who responded to glucocorticoid therapy and enrolled clinical remission (15). We tried prednisolone therapy for 4 weeks but did not obtain any benefit. Cyclophosphamide, azathiopyrine and plasmapheresis are other suggested treatment regimens (11, 18-20) but our patient did not give consent to any of them.

References

1. Goldstein BJ. Syndromes of extreme insulin resistance. In: Kahn CR, Weir GC, eds. Joslin's Diabetes Mellitus. 13th ed. Lea&Febiger Pennsylvania 1994, pp. 282-299.
2. Moller DE, Flier JS. Insulin resistance-mechanisms, syndromes, and implications. *N Engl J Med* **26;** 32513): 938-48, 1991.
3. Silver K, Shuldiner AR, Roth J. Insulin allergy and insulin resistance. In: Lichtenstein LM, Fauci AS eds. Current therapy in allergy, immunology and rheumatology. 5th ed. Missouri: Mosby Year Book Inc. 1996; pp 180-185.
4. Kahn CR, Rosenthal AS. Immunologic rections to insulin: Insulin allergy, insulin resistance, and the autoimmune insulin syndrome. *Diab Care* **2** (3): 283-295, 1979.
5. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N Engl J Med* **294** (14): 739-45, 1976.
6. Krook A, Kumar S, Laing I, Boulton AJM, Wass JAH, O'Rahily S. Molecular scanning of the insulin receptor gene in syndromes of insulin resistance. *J Engl J Med* **300** (8): 413-9, 1979.

7. Flier JS, Kahn CR, Roth J. Receptors, Antireceptor antibodies and mechanisms of insulin resistance. *N Engl J Med* **300** (8): 413-9, 1979.
8. Bar RS, Levis WR, Rechler MM- Harrison LC, Siebert C, Podskalny J, Roth J, Muggeo M. Extreme insulin resistance in ataxia telengiectasia. Defect in affinity of insulin receptors. *New Engl J Med* **298:** 1164-1171, 1978.
9. Taylor SI, Grunberger G, Marcus-Samuels B, Underhill LH, Dons RF, Ryan J, Roddam RF, Rupe CE, Gorden P. Hypoglycemia associaed with antibodies to the insulin receptor. *New Engl J Med* **307:** 1422-1426, 1982.
10. Taylor SI, Barbetti F, Acili D, Roth J, Gordden P. Syndromes of autoimmunity and hypoglycemia. Autoantibodies directed against insulin and its receptor. *Endocrinol and Metab Clin North Am* **18:** 123-143, 1989.
11. Eriksson JW, Bremell T, Eliasson B, Fowelin J, Fredriksson L, Yu ZW. Successful treatment with plasmapheresis, cyclophosphamide, and cyclosporin A in type B syndrome of insulin resistance. Case report. *Diabete Care* **21** (8): 1217-20, 1998.
12. Pulini M, Raff B, Chase EE. Insulin resistance and acanthosis nigricans. Report of a case with antibodies to insulin receptors. *Ann Intern Med* **85**(6): 749-51, 1976.
13. Flier JS, Bar RS, Muggeo M, Kahn CR, Roth J, Gorden P. The evolving clinical course of patients with insulin receptor autoantibodies: spontaneous remission or receptor proliferation with hypoglycemia. *J Clin Endocrinol Metab* **47** (5): 985-95, 1978.
14. Shimoyama R, Ray TK, Savage CR, Owen OE, Boden G. In vivo effects of antiinsulin receptor antibodies. *J Clin Endocrinol Metab* **59** (5): 916-23, 1984.
15. Magsino CH Jr, Spencer J. Insulin receptor antibodies and insulin resistance. *South Med J* **92** (7): 717-9, 1999.
16. Erikkson JW, Bremell T, Eliason B, Fowelin J, Fredrikson L, Yu ZW. Successful treatment with plasmapheresis, cyclophosphamide and cyclospoin A in type B syndrome of insulin resistance. Case report. *Diab Care* **21** (8): 1217-20, 1998.
17. Tsokos GC, Gorden P, Antonoych T, Wilson CB, Balow JE. Lupus nephritis and other autoimmune features in patients with diabetes mellitus due to autoantibody to insulin receptors. *Ann Intern Med* **102:** 176-181, 1985.
18. Sims RE, Rushford FE, Huston DP, Cunningham GR. Successful immunosuppressive therapy in a patient with autoantibodies to insulin receptos and immune complex glomerulonephritis. *S Med J* **80:** 903-906, 1987.
19. Muggeo M, Flier JS, Abrams RA, Harrison LC, Deisserroth AB, Kahn R. Treatment by plasma exchange of a patient with autoantibodies to the insulin receptor. *N Engl J Med* **300:** 477-480, 1979.
20. Kawanishi K, Kawamura K, Nishina Y, Goto A, Okada S, Ishida T, Ofuji T, Kahn CR, Flier JS. Successful immunosuppressive therapy in insulin resistant diabetes caused by anti-insulin receptor autoantibodies. *J Clin Endocrinol Metab* **44:** 15-21, 1977.