

Successful Treatment With Plasmapheresis, Cyclophosphamide, and Cyclosporin A in Type B Syndrome of Insulin Resistance

A case report

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CASE HISTORY— A woman born in 1949 was diagnosed in 1990 with systemic lupus erythematosus. She was treated with prednisolone, and <1 year later she presented with marked hyperglycemia. Large doses of insulin were given four times per day. Even though the patient was thin (BMI 17.4 kg/m²), very little improvement was seen.

INVESTIGATIONS AND TREATMENT— Serum insulin levels were high, and a euglycemic clamp investigation confirmed severe insulin resistance. The patient's serum contained insulin receptor antibodies inhibiting insulin binding, and thus the patient had a type B syndrome of insulin resistance. After diet and exercise, glycemic control stabilized and insulin treatment was withdrawn. However, in late 1993 she was in a catabolic and hyperglycemic state even though prednisolone doses were increased and azathioprin was added. In early 1994 she was treated with plasmapheresis and cyclophosphamide i.v. Subsequently, cyclosporin A was started as a maintenance therapy in addition to azathioprin. There was a rapid and sustained clinical improvement. Since late 1994 and onward, there is no sign of diabetes or glucose intolerance and there are no demonstrable insulin receptor antibodies in the patient's serum.

DISCUSSION— Severe type B insulin resistance may respond favorably to treatment with plasmapheresis and cyclophosphamide followed by cyclosporin A in combination with azathioprin.

Severe insulin resistance presenting in adults is often part of the type A or type B syndromes of insulin resistance (1). The type A syndrome, which usually occurs in young women, is due to genetic defects affecting the insulin receptor or other components in the insulin signaling machinery. The patients display marked hyperinsulinemia, possibly hyperglycemia, masculinization, and often acanthosis nigricans, a typical hyperkeratotic dark-pigmented skin lesion (2). Similar clinical features occur in insulin resistance syn-

drome type B, which is also found mainly in females. It is caused by polyclonal immunoglobulin (Ig) G-antibodies directed against the insulin receptor (3). The formation of antibodies is almost always part of another autoimmune disease, most often systemic lupus erythematosus (SLE). Several other disorders involving the immune system can also be associated with the type B syndrome (3,4). The antibodies block the binding of insulin to its receptor at the cell surface and thereby inhibit the effects of insulin. However, these antibodies often

also have an insulin-mimicking effect, which can cause spontaneous hypoglycemia, particularly during fasting (3).

CASE HISTORY— Our patient is a woman born in 1949 in whom microscopic hematuria was found in 1988. In 1989, she presented with butterfly rash on her face and urticaria of the limbs and trunk. She also experienced stiffness of several joints and increased loss of hair. Skin biopsy examination displayed urticaria vasculitis consistent with SLE. Further investigations in 1990 disclosed the presence of anti-DNA antibodies, anemia, leukopenia, and thrombocytopenia, as well as low levels of complement factors C3 and C4, and thus the SLE diagnosis was confirmed. In addition, a kidney biopsy showed morphological changes consistent with lupus nephritis. Treatment with prednisolone was initiated in June 1990, and shortly thereafter, chloroquine phosphate was added. The patient gradually began to experience increasing thirst and weight loss. In January 1991 glucosuria was discovered, but in fact it had also been present in May 1990 before the prednisolone treatment started.

INVESTIGATIONS AND TREATMENT

— The patient was admitted to a hospital in February 1991 with overt diabetes. She was very thin (BMI 17.4 kg/m²) but otherwise in a good general condition, and she showed no signs of virilization or acanthosis nigricans. Blood glucose was >20 mmol/l, and insulin treatment was initiated with four doses per day. The blood glucose level remained high (~15–20 mmol/l), even though large amounts of insulin were administered (~130 U/day, 2.7 U/kg body wt). Laboratory investigations in December 1991 showed high levels of insulin and C-peptide, indicating a high endogenous insulin production and insulin resistance. No significant difference between the levels of

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Abbreviations: SLE, systemic lupus erythematosus.

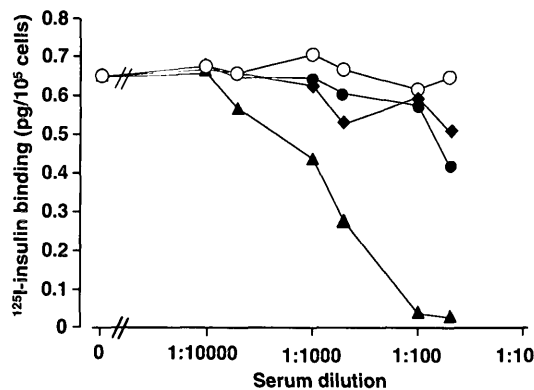


Figure 1—Effect of patient serum on ¹²⁵I-labeled insulin binding in rat adipocytes. Human ¹²⁵I-insulin (0.2 ng/ml) was added to isolated adipocytes for 60 min at 37°C together with serum from our patient (▲, ●, ◆) or from a normal control subject (○) at final dilutions as indicated. ¹²⁵I-insulin binding was assessed as previously reported (8). Patient serum was obtained just before treatment with plasmapheresis and cyclophosphamide (▲) and 2 months (●) and 3.5 years (◆) after treatment start, respectively.

total and free insulin in serum was found, suggesting that there were no insulin antibodies. A hyperinsulinemic euglycemic clamp was performed, and thus a fixed intravenous insulin infusion was given in parallel with glucose, which was adjusted to keep a constant normal blood glucose level (5). The amount of glucose infused corresponds to tissue glucose uptake and is used as a measurement of insulin sensitivity. The patient had a very low glucose uptake, thus reflecting severe insulin resistance. This finding also excluded a so-called subcutaneous insulin resistance syndrome, in which insulin resistance is seen upon subcutaneous but not intra-

venous insulin administration.

To test whether insulin receptor antibodies were present, the effect of patient serum on insulin binding to rat adipocytes was studied. It was found that the patient's serum, even at very high dilution, impaired insulin binding to its receptor (Fig. 1). With dot-blot assay, it was established that antibodies directed to the extracellular α -subunit of the insulin receptor were present (not shown). To study the metabolic impact of the antibodies, we measured glucose uptake in rat adipocytes in the presence of serum. The patient's serum alone had a weak enhancing effect on glucose uptake, but in contrast, insulin-stimulated glucose

uptake was clearly inhibited in a dose-dependent way by the serum (Fig. 2).

During the first part of 1992, the insulin treatment was gradually reduced and finally terminated. A diet containing a high amount of slowly absorbed carbohydrates was recommended. The patient practiced regular exercise, and her metabolic control improved, although blood glucose was still high in the evenings. She also gained some weight.

In spring 1993, the patient had an SLE relapse with tiredness, skin rash, and increased blood glucose levels. The prednisolone treatment was intensified, and high doses of gammaglobulin were administered to attempt to reduce B-cell activity and antibody synthesis. There was no clear improvement, and in October 1993, azathioprin treatment was initiated. The symptoms of SLE were reduced, but blood glucose continued to be high, and the patient was in a catabolic state with continuing weight loss.

To reduce the amount of insulin receptor antibodies by potent immune suppressing treatment, intravenous cyclophosphamide (500 mg) was given in January 1994, and in addition, plasmapheresis was performed three times. Cyclophosphamide infusions (1,000 mg) were then given on two additional occasions, but were terminated because of leukopenia and a suspected allergic reaction. Cyclosporin A was started as a follow-up treatment and is presently still ongoing. This

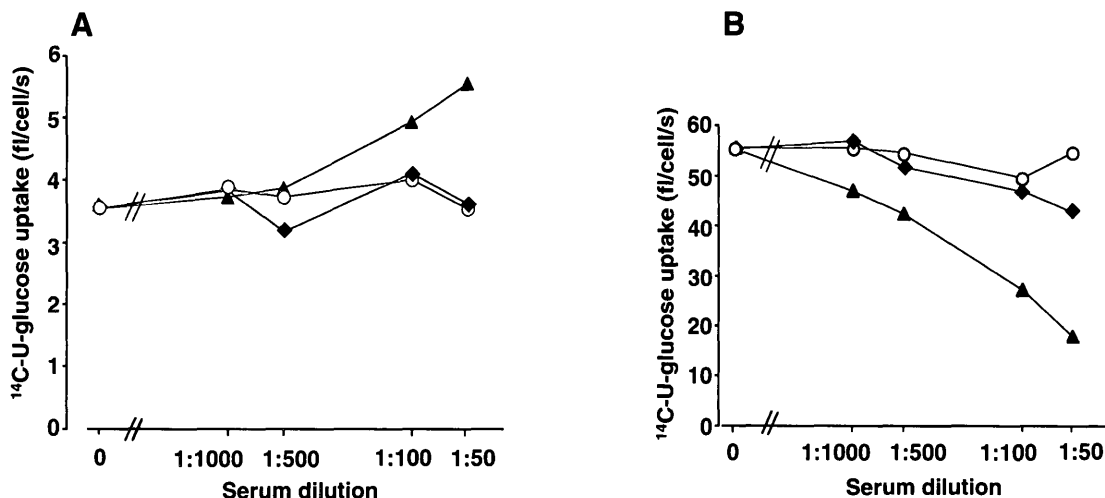


Figure 2—Effect of patient serum on [¹⁴C]glucose uptake in rat adipocytes. Isolated rat adipocytes were studied in glucose-free medium at 37°C either in the absence (A) or presence (B) of insulin (100 μ U/ml). Serum obtained from our patient just before (▲) or 3.5 years after (◆) treatment start or serum from a normal control subject (○) was present at final dilutions as indicated. After a 15-min incubation, D-[U-¹⁴C]glucose was added to the adipocyte suspension, and the incubation continued for another 60 min. Cellular clearance of [¹⁴C]glucose was assessed as previously described (9) and taken as an index of glucose transport rate.

Table 1—Laboratory findings and treatment 1990–1997

| Variable | Normal range | 1990 | | 1991 | | 1992 | | 1993 | | 1994 | | 1996 | 1997 |
|-----------------------------------|--------------|--------|------|--------|------|--------|------|--------|------|--------|------|------|--------|
| | | Spring | Fall | Spring | Fall | Spring | Fall | Spring | Fall | Spring | Fall | Fall | Spring |
| Whole blood HbA _{1c} (%) | 3.3–5.3 | | | 11.8 | 10.5 | 8.8 | 9.0 | 8.0 | 9.7 | 6.8 | 5.3 | 4.8 | 4.9 |
| Fasting serum insulin (mU/l) | <20 | | | >240 | >240 | >240 | | | | 99.1 | 14.3 | 8.5 | |
| Fasting serum C-peptide (nmol/l) | 0.2–1.5 | | | 3.1 | 3.5 | 2.1 | | 0.8 | 1.6 | 0.9 | 0.5 | 0.4 | |
| Serum-anti-DNA (kU/l) | <12 | 52 | >100 | 75 | 46 | 35 | | 82 | 65 | 47 | 46 | | |
| Treatment | | | | | | | | | | | | | |
| Prednisolone | | ————— | | | | | | | | | | | |
| Chloroquine phosphate | | ————— | | | | | | | | | | | |
| Gammaglobulin | | | | | | | | | — | | | | |
| Azathioprin | | | | | | | | | | | | | —————→ |
| Cyclophosphamide | | | | | | | | | | — | | | |
| Cyclosporin A | | | | | | | | | | | | | —————→ |
| Plasmapheresis | | | | | | | | | | — | | | |
| Insulin | | | | ————— | | | | | | | | | |

therapeutic approach resulted in increasing weight and a decrease in blood glucose levels. Moreover, during spring 1994, there was a clinical improvement of the patient's SLE, and the level of anti-DNA antibodies was clearly reduced from ~70 to ~40 kU/l (examples are shown in Table 1). During the rest of 1994, blood glucose was usually between 3 and 10 mmol/l, and the patient sometimes had hypoglycemic symptoms during fasting. HbA_{1c} was within the normal range, and an oral glucose tolerance test in December 1994 showed normal glucose tolerance. Fasting blood glucose levels were, at that time, quite low (3.2–3.6 mmol/l). According to World Health Organization criteria, the patient thus no longer had diabetes. Insulin and C-peptide levels were reduced significantly during 1994, indicating an improved insulin sensitivity. The improvement of the metabolic state was sustained through 1995–1997 and at present, 4 years after treatment start, the patient shows no signs of relapse of severe insulin resistance or diabetes. Moreover, her SLE is under relatively good control. The present treatment regimen (December 1997) is cyclosporin A (150–200 mg per day) and azathioprin (150 mg per day). Prednisolone was terminated in 1996. Reassessment of the patient's serum with respect to interaction with insulin binding and glucose uptake shows a complete normalization compared with the findings before the successful treatment (Figs. 1 and 2). Thus, there now seem to be no insulin receptor antibodies present.

Table 1 summarizes laboratory findings and treatment during 1990–1997.

DISCUSSION — Patients with the type B syndrome of insulin resistance have previously in some cases been successfully treated with immune-modulating therapy, such as cyclophosphamide and plasmapheresis (2,6). However, the beneficial effects following such treatment may be temporary, and with time, relapses may occur. In our patient, this regimen appears to have been successful in promoting the disappearance of the insulin receptor antibodies, but we also wished to provide a prophylactic long-term immune-modulating therapy. Therefore, we tried a follow-up treatment with chronic administration of cyclosporin A in combination with azathioprin to suppress both T- and B-cell proliferation (7). B-cell production of autoantibodies is often T-cell dependent, and this treatment might lead to a continuing repression of the synthesis of insulin receptor antibodies. The clinical and experimental investigations in our patient suggest that the therapeutic approach used was successful, and that a long-term effect is still present after >4 years. The treatment appears to have produced a sustained amelioration in the general SLE activity, as well as in the production of insulin receptor antibodies. Thus, the modulation of autoimmune activity was not selective with respect to type B insulin resistance, but instead probably occurred via a more general lymphocyte suppression. In severe cases of type

B insulin resistance, we suggest that plasmapheresis and cyclophosphamide can be used to achieve short-term suppression of insulin receptor antibodies and that cyclosporin A in combination with azathioprin can be tried as a chronic maintenance treatment to prevent relapse of the disorder.

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