

Type B insulin resistance syndrome in a patient with type 1 diabetes

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Summary

Type B insulin resistance syndrome (TBIRS) is a very rare autoimmune disorder with polyclonal autoantibodies against the insulin receptor, resulting in severe and refractory hyperglycemia. Described here is a patient who within a few months after the onset of autoimmune type 1 diabetes increased her insulin requirements more than 20-fold; despite this she had considerable difficulty maintaining a plasma glucose value of <40–60 mmol/L (720–1100 mg/dL). On suspicion of TBIRS, the patient was started on tapering dose of glucocorticoids to overcome the autoimmune insulin receptor blockade, resulting in an immediate and pronounced effect. Within days, insulin requirements decreased by 80–90% and plasma glucose stabilized around 7–8 mmol/L (126–144 mg/dL). The presence of antibodies to the insulin receptor was detected by immunoprecipitation and binding assays. After a 4-month remission on low maintenance dose prednisolone, the patient relapsed, which required repeated plasmaphereses and immune column treatments with temporarily remarkable effect. Mixed and transient results were seen with rituximab, mycophenolic acid and bortezomib, but the glycemic status remained suboptimal. Lack of compliance and recurrent infections may have contributed to this.

Learning points:

- Type B insulin resistance syndrome (TBIRS) is a very rare autoimmune disorder with acquired polyclonal autoantibodies against the insulin receptor, resulting in severe and refractory hyperglycemia.
- We describe here a young patient in whom, a few months after the onset of a regular autoimmune diabetes, insulin requirements in a short time increased more than 20-fold, but despite this, the plasma glucose level could be kept at <40–60 mmol/L only with considerable difficulty. Did this patient have TBIRS?
- On suspicion of TBIRS, the patient was started on tapering glucocorticoids to overcome the autoimmune insulin receptor blockade, resulting in an immediate and pronounced effect; within days insulin requirements decreased by 80–90% and plasma glucose stabilized around 7–8 mmol/L.
- The presence of antibodies to the insulin receptor was detected by immunoprecipitation and binding assays.
- After a 4-month remission on low maintenance dose prednisolone, the patient relapsed, which required repeated plasmaphereses with temporarily remarkable effect.
- TBIRS should be considered in diabetic patients whose glycemia and/or insulin requirements are inexplicably and dramatically increased.

Background

Resistance to insulin is becoming more common than ever, as the prevalence of obesity is increasing in the population. This ‘natural’ or lifestyle-caused insulin resistance is an important and driving pathogenic factor for the onset of prediabetes and overt type 2 diabetes in genetically predisposed individuals.

Type B insulin resistance syndrome (TBIRS) is a very rare autoimmune disorder with acquired polyclonal autoantibodies against the insulin receptor, which results in severe and refractory hyperglycemia (1). We describe here a young patient in whom, a few months after the onset of a regular autoimmune diabetes, insulin requirements in a short time increased more than 20-fold, but despite this her P-glucose could be kept <40–60 mmol/L (720–1100 mg/dL) only with considerable difficulty. Informed consent has been obtained from the patient.

Case presentation

The onset of autoimmune diabetes

The patient is a female in her thirties of Caucasian ethnicity. She came to the emergency room in 2011 (then 25 years old) because of new-onset diabetes with classic catabolic symptoms during the past few weeks. The patient’s grandfather had had diabetes of unknown type, but otherwise there was no known family history of metabolic disease; however, there was extensive family history of premature ischemic heart disease on the maternal side. Routine biochemistry revealed hyperglycemia with non-fasting plasma glucose of 19 mmol/L (342 mg/dL) and 4+ glucosuria, no acidosis but 2+ ketonuria. BMI was 36 kg/m².

The patient was admitted to the hospital and was started on mealtime direct-acting insulin analog t.i.d. and bedtime NPH-insulin. Glycemic control was swiftly normalized and the patient was discharged on a daily insulin dose of 28 U (0.3 U/kg). The long-term glycemic control was, as expected, poor with B-HbA_{1c} of 119 mmol/mol (13.0% (DCCT standard)). The serum concentration of C-peptide was initially 1.65 nmol/L (4.97 ng/mL). Blood pressure, renal function, urine albumin/creatinine ratio and retinopathy screening were unremarkable. The patient was discharged and scheduled to attend the outpatient clinic. After discharge, results from the analyses of autoantibodies against β-cell antigens arrived (GAD-65 >250 U/mL (ref. <5 U/mL), IA-2 negative).

Rapid development of progressive and severe insulin resistance

After merely a few months of stable glycemia, essentially unchanged insulin doses and gradually decreasing HbA_{1c} to 64 mmol/mol (8.0%), glycemic control began to deteriorate. The patient increased her insulin doses, but it became increasingly difficult to maintain glucose control despite high doses of insulin. No apparent reason for this deterioration was found. See Fig. 1 for a view of glycemic control and insulin needs over time.

The situation gradually became more desolate and the patient ended up in a highly catabolic state with severe hyperglycemia, weight loss, severe fatigue, constant headache, polydipsia and increasingly frequent polyuria. The situation escalated further during 2014, with marked deterioration in glycemic control (HbA_{1c}: 100 mmol/mol (11.3%)) despite high insulin doses (>100 U/day). She showed no lipo-hyper- or dys-trophies at the different injection sites. When the patient was hospitalized, diabetes nurses noted proper injection technique and the same poor effect of insulin resulted when insulin was administered by the nurses. Analysis of insulin antibodies was negative on two occasions. Monogenic diabetes (MODY 1–3) was also excluded. Plasma levels of adiponectin (11 mg/L (ref. 6–25)), IGFBP-1 (4.6 μg/L (ref. 0.3–14)) and SHBG (44 nmol/L (ref. 32–128)) were normal. Adiponectin levels are oftentimes raised under conditions of severe insulin resistance (1); however, it is also known that hyperglycemia *per se* may lower the levels (2). Other endocrine analyses (thyroid, adrenals, DHEA,

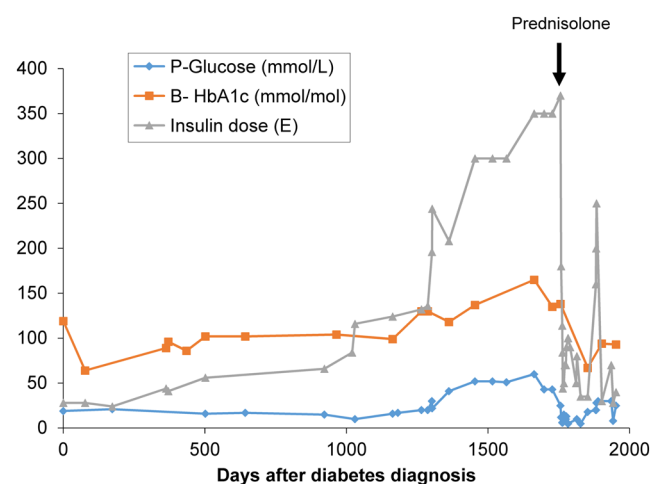


Figure 1 Changes in the patient’s insulin requirements and glycemic control over time. The time course of the patient’s insulin requirements and glucose control since the onset of her diabetes is shown. Arrow indicates start of glucocorticoid treatment.



GH, IGF-1, proinsulin, glucagon, testosterone, prolactin, FSH and LH) were also within normal ranges.

In the home clinic, the county hospital and university hospital, the patient had during the past 4 years *ex juvantibus* been prescribed high doses of drugs from all anti-diabetic classes available on the market, such as metformin, pioglitazone, acarbose, sitagliptin, liraglutide and dapagliflozin in different combinations, with and without a number of different insulin regimens or types in very high doses, without any noticeable effect. No difference in glycemia was discernable when insulin was given i.m. or by radically lower insulin doses.

Suspicion of TBIRS and instant effect of glucocorticoids

In late 2015, the situation was worse than ever: The glycemic control was, despite 370 U of insulin s.c. per day (6.7 U/kg) (at diagnosis: 28 U/day (0.3 U/kg, i.e. >20-fold increase in insulin needs)), totally deranged with fasting plasma glucose >35 mmol/L (>630 mg/dL), non-fasting plasma glucose of 50–60 mmol/L (900–1100 mg/dL) and HbA_{1c} of 165 mmol/mol (17.2%). Despite this, the patient was amazingly unaffected. Her BMI was 22 kg/m² (before diabetes onset: 36 kg/m²).

Suspicion of TBIRS now arose. The patient was put on tapering dose of glucocorticoids to break the autoimmune insulin receptor blockade that characterizes TBIRS. After initiation of 60 mg prednisolone q.d., the situation quickly and markedly improved: Within 3 days the insulin dose had to be reduced by 75% to avoid hypoglycemia, a reduction that for the same reason continued and glycemia quickly stabilized around 6–7 mmol/L (110–126 mg/dL) on an insulin dose of approximately 40 U/day. The patient's daily dose of prednisolone was tapered by 10 mg/week to a maintenance dose of 5 mg q.d. No other stigmata of insulin resistance, such as hirsutism or *acanthosis nigricans*, were noted.

At revisiting the outpatient clinic 1 month after the start of steroid treatment, the patient reported a clear improvement in quality of life.

Autoantibodies to the insulin receptor detected

Before the patient was started on glucocorticoid treatment, samples were frozen pending analysis of insulin receptor antibodies. The analyses were performed by immunoprecipitation (3) and binding assay (4), respectively. The results showed presence of insulin receptor antibodies in the patient's serum and a decrease by

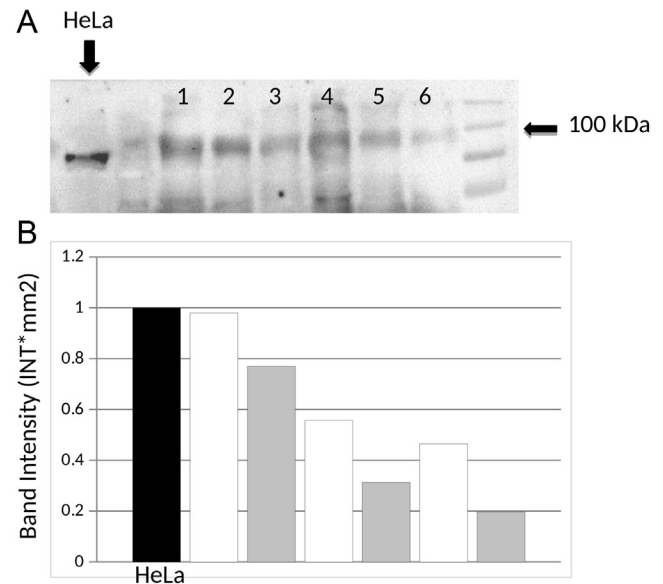


Figure 2 Presence of insulin receptor antibodies in patient serum is decreased by glucocorticoid treatment. (A) A representative blot from SDS-PAGE analysis of immunoprecipitation eluates indicates the presence of IR antibodies in patient serum samples. From left to right: HeLa cell lysates (positive control); buffer (negative control); Lane 1: patient serum day 1 before prednisolone; Lane 2: patient serum day 1 after prednisolone; Lane 3: patient serum day 2 before prednisolone; Lane 4: patient serum day 2 after prednisolone; Lane 5: patient serum day 3 before prednisolone; Lane 6: patient serum day 3 after prednisolone. Densitometric quantifications of bands in A indicate that the amount of IR antibodies present in serum samples is reduced by prednisolone treatment (B). Black - HeLa cell lysates; white bars - before prednisolone treatment; gray bars - after prednisolone treatment.

glucocorticoid treatment (Fig. 2A and B). To test whether patient serum contained antibodies blocking the insulin receptor, the effect of serum to inhibit insulin binding to adipocytes was investigated (Fig. 3A and B). Isolated s.c. human adipocytes from a healthy subject were incubated with serum from the patient obtained before the initiation of therapy with plasmapheresis and rituximab or with serum from a healthy control subject, at various dilutions before adding ¹²⁵I-insulin (Fig. 3A). The results showed that serum from the patient inhibited insulin binding to adipocytes by up to 40%, compared with control serum. This supports the view that the patient serum contains anti-insulin receptor antibodies blocking insulin binding to its cell surface receptors and insulin action. The insulin-binding assay was repeated about 5 months after initiation of rituximab therapy and plasmaphereses. Control serum or patient serum obtained just before and after a plasmapheresis session, respectively, was present as indicated (Fig. 3B). At this point, insulin binding was not inhibited by the patient's serum and there was no

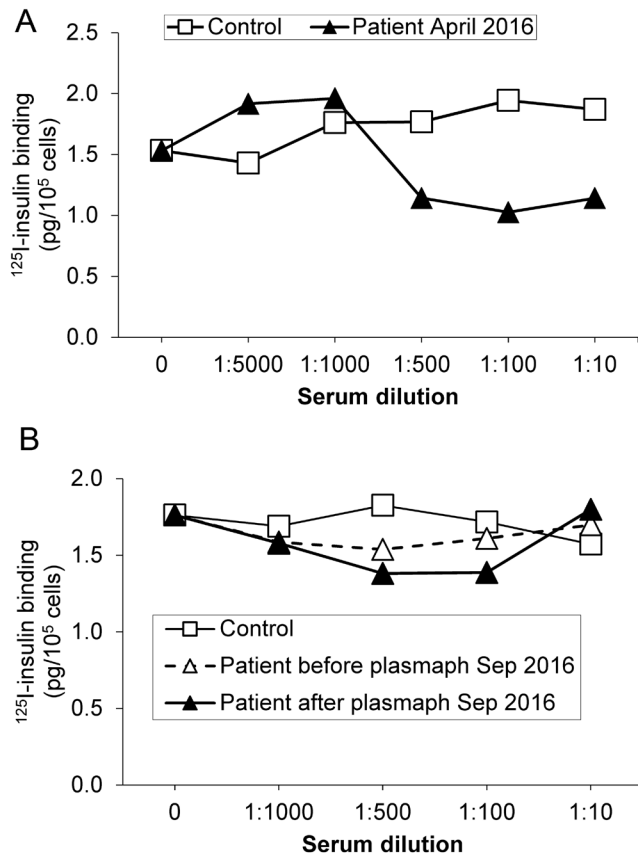


Figure 3 Effects of patient serum on ¹²⁵I-insulin binding to adipocytes prior to initiation of therapy and in conjunction with plasmapheresis. (A) Human adipocytes were incubated with serum from the patient or from a healthy control person (normal weight young woman) in indicated dilutions as well as with human ¹²⁵I-insulin. This was done before starting treatment in April 2016 to evaluate the binding of insulin to its receptor (4). (B) ¹²⁵I-insulin binding was repeated with serum obtained in September 2016, both shortly before and immediately after treatment with plasmapheresis.

change following this specific plasmapheresis procedure. Healthy subjects donated serum and s.c. adipose tissue for the purpose of diabetes research (approved by the Uppsala Regional Ethics committee, Dnr 2013/183).

Recurrence of TBIRS

A maintenance dose of prednisolone 5 mg/day worked well for 4 months. Then glucose control worsened, despite substantial increases in insulin doses (~250 U/day) and increasing the dose of prednisolone to 20 mg/day. Because of this relapse, the patient was subjected to a series of three plasmaphereses with immediate normalization of glycemia and insulin doses to 'premorbid' levels, strengthening the suspicion of

circulating autoantibodies to the insulin receptor. She continued with 20 mg/day prednisolone but relapsed again, only 4–5 weeks after the plasmaphereses and later underwent additional plasmaphereses. The plasmaphereses reduced insulin requirements, but after a while the effect became less noticeable. As a result, we tested immunoadsorption (Globaffin column), which allows treatment of larger plasma volumes, but this did not improve glucose control. Mixed and short-lived results were seen with rituximab, mycophenolic acid and bortezomib, and the glycaemic state is essentially unchanged compared to when the patient received her TBIRS diagnosis, possibly due to lack of compliance, recurrent infections, her type 1 diabetes and ongoing TBIRS. After various attempts at immune-modulating treatment, the patient is on a stable low dose of prednisolone, 5 mg q.d. Due to difficulties in optimizing the insulin injection therapy, she has started s.c. insulin infusion with an insulin pump with some improvement in glycaemic control which persists to this day.

Discussion

Pathogenesis

TBIRS is an extremely rare condition characterized by acquired antagonistic autoantibodies to the insulin receptor, whose effects are quantitatively most noticeable in skeletal muscle, liver and adipose tissue (1, 5). The occurrence is so extremely low that population studies cannot be done, so the exact prevalence remains unknown (a search for 'type B insulin resistance' on PubMed yielded only 75 hits between 1983 and 2019). For an estimate it can be mentioned that an NIH clinic in Bethesda, which seems to be a regional referral center for the U.S. East Coast, only handled 24 patients between 1973 and 2000 (5), that is, not even one case per year.

TBIRS was coined as a separate entity by Jeffrey S Flier, who more than 40 years ago discovered the syndrome and its cause during his postdoctoral research in Prof C Ronald Kahn's laboratory at the Joslin Diabetes Center in Boston (6).

The degree of insulin resistance that affected our patient pales in light of some other published cases, where as much i.v. insulin as 30 000 U/day (3) or even 150 000 U/day (7) – that is, 1.5 L of concentrated insulin per day – was unable to affect the hyperglycemia in the least. These astronomical, yet completely ineffective, doses of insulin let us imagine the potency and affinity of the insulin receptor antibodies.



Comorbidity with other autoimmunopathies

In the literature, TBIRS oftentimes co-exists with other autoimmune disorders (1). SLE appears to be conspicuously common in these individuals, and it is speculated that the outbreak of such autoimmunopathies somehow also triggers the generation of autoantibodies against the insulin receptor. Our patient was negative for antibodies against mitochondrial antigen, nuclear antigens, parietal cell antigens, citrulline, extractable nuclear antigen, liver/kidney microsome type 1, myeloperoxidase anti-neutrophilic cytoplasmic antigens, proteinase-3 anti-neutrophilic cytoplasmic antigens, rheumatoid factor, soluble liver antigen/liver pancreas antigen, smooth muscle antigens, thyroperoxidase and tissue transglutaminase and for HIV, viral hepatitis and *H pylori*.

It is conceivable that the patient's autoimmune type 1 diabetes triggered the emergence of autoantibodies against insulin receptor too. One other case of TBIRS in a patient with type 1 diabetes has been reported (8).

Prognosis and the risk of severe hypoglycemia

Untreated, the long-term prognosis for TBIRS-patients generally is very poor with a 10-year mortality of approximately 50% (1, 5). Death usually occurs from complications of intractable hypoglycemia. This may seem paradoxical, but is explained by the autoantibodies, which may also act agonistic at the insulin receptor (9). Chronic severe hyperglycemia and other manifestations of profound insulin resistance on the other hand carry well-known risks of angiopathy. Our patient has had her TBIRS for 7 years and she also has a strong heredity of premature ischemic heart disease.

Treatment

As TBIRS is such an utterly rare condition, the treatment has traditionally been empirical and several anecdotal reports of therapeutic efforts with glucocorticoids, rituximab, cyclophosphamide, cyclosporine A, azathioprine and plasmapheresis have been published (1, 3, 4). Evidence-based treatments have been lacking and so many interventions have been based on the principle of 'trial and error'. However, positive results of combined immune-modulating treatments were recently reported in a prospective clinical study in TBIRS patients (10). In our patient, immunomodulatory treatments had an initial

positive effect, which, however, unfortunately rapidly subsided.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

Å S provided care for the patient, wrote and edited the manuscript. J S provided care for the patient. M J P, T N, T L, P K and J W E provided care for the patient and edited the manuscript. The authors thank Honar Dylman and Prof Lars Rönnblom for valuable advice regarding the immunosuppressive treatment.

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