

Treatment of type B insulin resistance with immunoglobulin: novel use of an old therapy

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TO THE EDITOR: Type B insulin resistance is an uncommon syndrome characterised by abnormal glucose homeostasis (hypo- and/or hyperglycaemia), the presence of insulin receptor (IRec) autoantibodies, and intact IRec structure. It occurs mostly in African Americans, often with coexisting autoimmune disease.¹

We report a case of type B insulin resistance with atypical features. A 44-year-old white male with a 22-year history of poorly controlled diabetes was referred to us with severe Graves ophthalmopathy. His home blood glucose levels ranged from 3.0 to 25.0 mmol/L (reference range [RR], 3.5–5.5 mmol/L) and he required over 800 units of insulin daily. His ophthalmic condition had been diagnosed 18 months earlier and had been observed until its recent deterioration into diplopia.

Examination confirmed severe bilateral Graves ophthalmopathy, with 6/6 visual acuity bilaterally, and euthyroidism. Thyroid function tests showed the following levels: thyrotropin-stimulating antibody, 69 U/mL (RR, < 10 U/mL); thyroid-stimulating hormone, 2.3 mU/L (RR, 0.4–4.0 mU/L); and free tetraiodothyronine, 18.5 pmol/L (RR, 10.2–24.5 pmol/L). Routine biochemical and immunological studies were normal.

Orbital magnetic resonance imaging showed marked ocular muscle hypertrophy and adipose tissue congestion, consistent with Graves ophthalmopathy. After 3 months of combination immunosuppressant therapy, the patient showed minimal improvement. In view of his diabetes, he was commenced on intravenous immunoglobulin rather than a glucocorticoid. Within 24 hours, he developed marked hypoglycaemia, with a glucose level of 2.1 mmol/L. Despite ceasing insulin treatment, the patient's home blood glucose levels hovered between 4 and 6 mmol/L for the next 7–10 days. This continued until Day 14, when small doses of insulin were required, escalating to about 800 U/day before the next course of intravenous immunoglobulin. A clinical diagnosis of type B insulin resistance was made.

The clinical picture suggested the presence of dual stimulating and blocking autoantibodies in the presence of structurally intact IRecs. At maximal insulin resistance, the IRec concentration is thought to be normal, but probably with reduced affinity. The blocking

antibodies are believed to be polyclonal.² The pathophysiology of the hypoglycaemic phase is unknown, but the antibodies would need to behave as IRec stimulators, possibly via partial agonism and increased IRec numbers.³ The mechanism of the selectivity of intravenous immunoglobulin therapy and its preferential removal of the inhibitory autoantibodies is yet to be unravelled. Proposed mechanisms include suppression of the inhibitory antibody activity and modulation of the immune system in favour of IRec-stimulating (hypoglycaemia-inducing) autoantibodies. Treatments include immunosuppression, plasmapheresis and rituximab therapy.^{4,5}

As far as we are aware, the incidental but favourable response to intravenous immunoglobulin described here has not been previously observed. Our report highlights the atypical characteristics of this fascinating syndrome, including male sex, European ethnicity and a novel treatment modality.

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