OBSERVATIONS

Anti-Insulin Receptor Antibodies Related to Hypoglycemia in a Previously Diabetic Patient

JEAN-CHRISTOPHE MAIZA, MD[1]
MARTINE CARON-DEBARLE, MD[2,3]
CORINNE VIGOUROUX, PHD[2,3,4]
STÉPHANE SCHNEEBELI, MD[1]

From the [1]Department of Endocrinology and Metabolic Diseases, Hospital Groupe Hospitalier Sud Reunion, Saint-Pierre, France; [2]Pierre et Marie Curie University-Paris 6, UMR_S938, Paris, France; [3]INSERM, UMR_S 938, Saint-Antoine Research Centre, Paris, France; and the [4]Department of Clinical Biochemistry and Hormonology, Hospital Tenon, Paris, France.

Corresponding author: Jean-Christophe Maiza, jean-christophe.maiza@chu-reunion.fr.

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We report the case of a 47-year-old woman who was referred to our unit for hypoglycemia. She was diagnosed with diabetes at age 30 years and was previously treated with metformin, sulfonylureas, and glucagon-like peptide 1 agonists. Despite interruption of her treatments, she had for 1 month clinical features evoking hypoglycemic spells, with adrenergic and neuroglycopenic symptoms subsiding after glucose administration. Her BMI was 23.8 kg/m^2. She had axillary acanthosis nigricans but no lipodystrophy. Continuous glucose monitoring showed hypoglycemia down to 2.1 mmol/L, mostly during fasting periods, and hyperglycemia up to 13.7 mmol/L in the absence of any treatment. HbA_{1c} was 15%. During a fasting test, venous glucose concentration dropped to 2.5 mmol/L with concomitant low serum levels of C-peptide, insulinemia, and proinsulinemia: <1.40, <3, and 3.6 pmol/L, respectively (reference ranges in healthy subjects 17.8–173, 370–1,470, and 3.3–28 pmol/L, respectively). Plasma levels of cortisol, somatostatin, IGF-1, and Western blot analysis of IGF-2 and its precursors were normal. Thoracoabdominal computed tomography and whole-body F-18-fluorodeoxyglucose positron emission tomography scan did not reveal any abnormality.

We evaluated the presence of anti-insulin receptor antibodies (AIRAs) using a radioreceptor assay (1). The patient's total serum and purified immunoglobulin fractions inhibited the binding of a tracer concentration of radiolabeled insulin, consistent with significant titers of AIRAs. Patient's serum and purified immunoglobulins activated proximal (tyrosine phosphorylation of insulin receptor β-subunit and insulin receptor substrate-1) and distal (phosphorylation of Akt/PKB) insulin-signaling pathways in vitro in a dose-dependant manner, mimicking insulin action.

There was no clinical evidence of either systemic lupus erythematosus or another autoimmune disease, and the search for anti-nuclear, anti-DNA, antithyroid, anti-GAD, and anti-insulin antibodies was negative. Serum protein electrophoresis was also normal. A high-dose corticosteroid therapy (1 mg/kg prednisone) was introduced for 1 month with a progressive decrease over 4 months, which allowed a complete disappearance of hypoglycemic events. Because of persistent hyperglycemia, decreasing doses of corticosteroid were associated with insulin therapy. Search for serum AIRA after 3 months of treatment was negative.

The occurrence of non–insulin-mediated hypoglycemia requires the search for tumors secreting somatostatin, IGF-1, IGF-2, or its precursors (2). After having ruled out those diagnoses, we detected serum AIRAs that activated insulin signaling in our patient. The concomitant disappearance of hypoglycemia and AIRAs after corticosteroid therapy strongly suggested that AIRAs were the cause of hypoglycemias. In most reported cases, AIRAs have been shown to occur in a context of autoimmune-associated disease—mostly preexisting systemic lupus erythematosus, primary biliary cirrhosis, or Hashimoto thyroiditis. AIRAs were generally responsible for rapidly progressive insulin-resistant diabetes, sometimes associated with spontaneous hypoglycemia with hyperinsulinemia that could be due to an impairment of insulin degradation (3,4). In our patient, we could not rule out the responsibility of preexisting AIRAs in the development of diabetes, and AIRAs did not induce hyperinsulinemia. First-line treatment is usually corticosteroid therapy, but the therapeutic strategies are not well defined because of the rarity of the disease (4). Our report highlights the fact that non–insulin-mediated hypoglycemia must lead to the search of AIRAs even in case of preexisting long-lasting diabetes and in the absence of autoimmune-associated disease.

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