# Intractable Hypoglycemia in the Setting of Autoimmune Overlap Syndrome

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Evaluation of hypoglycemia in a patient with known diabetes mellitus, although usually straightforward, can at times be challenging. We present the case of an 8 year-old Latina girl initially diagnosed with type 1 diabetes mellitus in the setting of multiple autoimmune disorders, including dermatomyositis and lupus nephritis. She subsequently developed signs of insulin resistance and severe hypoglycemia, which was found to be due to insulin-receptor autoantibodies. This condition, known as type B insulin resistance, is a rare, heterogeneous metabolic disease that may feature hypoglycemia in the setting of extreme insulin resistance and hyperinsulinemia and, in this case, masqueraded as type 1 diabetes mellitus. The presence of hypoglycemia in the setting of multiple autoimmune disorders should prompt consideration of autoimmune-mediated hypoglycemia. In addition to immunologic modifying therapies, advances in diabetes care in the form of continuous glucose monitoring have provided an additional tool to manage recurrent hypoglycemia.

Autoimmune hypoglycemia syndromes are rare causes of hypoglycemia in children, characterized by elevated levels of insulin and antibody-mediated hypoglycemia. The predominance of signs of insulin resistance and hyperandrogenism, concomitant presence of rheumatologic disease, and poor response to therapy suggest type B insulin resistance.[1,2] In this case report, we describe a case of an 8-year old girl with type B insulin resistance, which was initially thought to be type 1 diabetes mellitus (DM). This case report illustrates the utility of advanced technology, such as continuous glucose monitoring (CGM) and novel immunotherapy, in the management of hypoglycemia.[3]

## CASE REPORT

An 8 year-old Latina girl with a history of dermatomyositis managed on steroids presented with polyuria and polydipsia, a random blood glucose (BG) level of >200 mg/dL, and elevated hemoglobin A1C of 7.3%. She had been on a prednisone dose of 15 mg (0.8 mg/kg) daily, however, she was diagnosed with type 1 DM based on a highly elevated GAD-65 autoantibody level (Table 1) and was started on 1.1 U/kg per day of insulin. After her DM diagnosis, she developed systemic lupus erythematosus (SLE) along with glomerulonephritis.

Three months later, the patient was admitted to the hospital with refractory hypoglycemia despite cessation of insulin therapy. Her hemoglobin A1C decreased from 7.3% to 5.6%. During the course of her admission, she had wide excursions in BG, with postprandial hyperglycemia > 300 mg/dL and early morning hypoglycemia <50 mg/dL (Fig 1). Her autoimmune disease–related medical history is shown in Table 1.

On examination, her weight was 20.7 kg (7th percentile), her height

## abstract

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**DOI:** 10.1542/peds.2016-0866

Accepted for publication Nov 29, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).



**FINANCIAL DISCLOSURE:** Dr Semple is supported by a Senior Research Fellowship from the Wellcome Trust grant WT098498. The other authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** Dr Semple is funded by the Wellcome Trust (grant WT098498), the UK Medical Research Council (MRC_MC_UU_12012/5) and the United Kingdom National Institute for Health Research, Cambridge Biomedical Research Centre.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**To cite:** Shanker K, Daley T, Semple R, et al. Intractable Hypoglycemia in the Setting of Autoimmune Overlap Syndrome. *Pediatrics.* 2017; 139(6):e20160866

was 116.5 cm (2nd percentile), and her BMI was 15.2 kg/m$^2$ (36th percentile). She had a heart rate of 113 beats per minute, respiratory rate of 20/minute, and her blood pressure was 110/73 mm Hg. She had a thin body habitus, acanthosis nigricans in multiple body folds (Fig 2A), hypertrichosis on the face and shoulders, and swelling of the finger tips (Raynauds phenomenon). She was prepubertal, without evidence of adrenarche; otherwise, her physical examination was unremarkable.

A fasting study to understand the etiology of her hypoglycemia was performed in a supervised clinical environment (Table 2). She became hypoglycemic 5 hours after start of the fast, with suppressed ketones, suppressed free fatty acids, and a positive response to glucagon stimulation at the time of low blood glucose, all of which are indicative of insulin-mediated hypoglycemia. In addition to elevated insulin and C-peptide, laboratory studies revealed paradoxical hyperadiponectinemia of 24.4 mg/L and normal triglyceride levels of 109 mg/dL. An ultrasound showed increased bilateral ovarian enlargement with multiple cysts (Fig 2B).

**TABLE 1** Autoimmune Profile of the Patient

| Disease | Abnormal Biochemical Markers (Normal Range) | Additional Findings |
|---|---|---|
| Dermatomyositis | Aldolase: 11 U/L (3.3–9.7)<br>LDH: 866 U/L (420–750)<br>von Willebrand factor Ag: 249% (44–144) | Bilateral heliotrope rash<br>Gottron's papules<br>Proximal muscle weakness and tenderness |
| SLE | ANA: 1:640 (<1:40)<br>Anti-double stranded DNA Ab: 1:40 (<1:10)<br>Proteinuria:100 mg/dL (<10)<br>C4: <2 mg/dL (13–37)<br>C3: 19 mg/dL (90–200)<br>CH50: 0<br>Renal biopsy, membranous lupus nephritis, class V lupus nephritis | Facial swelling |
| Type 1 DM | GAD-65 Ab: 184.3 U/mL (<5.0)<br>IA-2 Ab: <0.8 U/mL (0–0.8)<br>Urine glucose: 1000 mg/dL (<10)<br>Blood glucose: 510 mg/dL | Presented with polyuria and polydipsia |
| Autoimmune thyroiditis | Anti-thyroid peroxidase Ab: 37.8 IU/mL (<9.0)<br>Thyroglobulin Ab: 57.5 IU/mL (<4) | Normal thyroid function, no symptoms and signs suggestive of thyroid dysregulation |
| Type B insulin resistance | Insulin receptor Ab positive by Western blot | Hypoglycemia, acanthosis nigricans, ovarian enlargement |

ANA, antinuclear antibody; CH50, total complement level; GAD-65, glutamic acid decarboxylase-65; IA-2, islet antigen 2; LDH, lactate dehydrogenase.

## DISEASE COURSE

Given the patient's diagnosis of DM, insulin overtreatment was considered the cause of her hypoglycemia. Despite insulin withdrawal, she continued to have hypoglycemia. The differential diagnosis included adrenal insufficiency, however, she was receiving supraphysiologic steroids for her SLE. With signs of insulin resistance, fasting hypoglycemia, and postprandial hyperglycemia, we postulated the presence of autoantibodies against the insulin receptor. Laboratory evaluation confirmed the presence of insulin

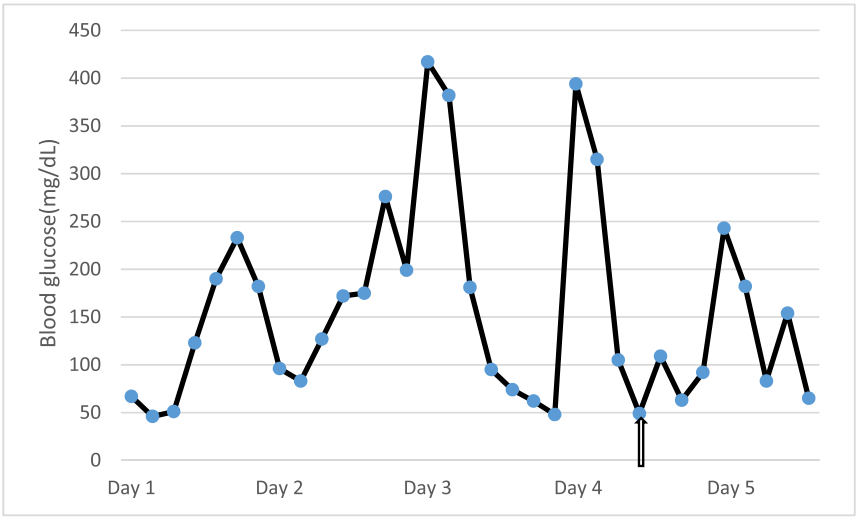


**FIGURE 1**
Blood glucose profile during hospital stay. Arrow indicates glucagon administration at the time of hypoglycemia, with resultant increase in blood glucose from 49 mg/dL to 109 mg/dL, suggestive of insulin-mediated hypoglycemia.

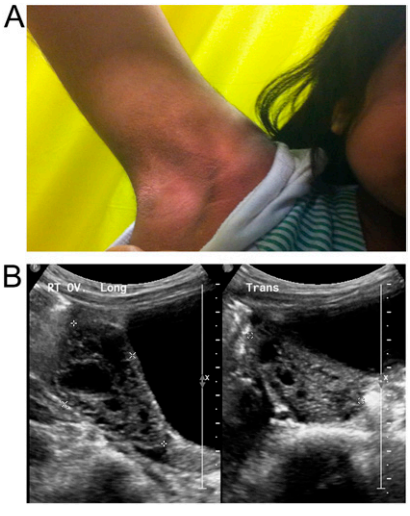


**FIGURE 2**
Clinical features of insulin resistance. A, Axillary acanthosis nigricans. B, Enlarged ovaries with multiple ovarian cysts; left ovary, 21.6 cm$^3$, right ovary, 25.3 cm$^3$

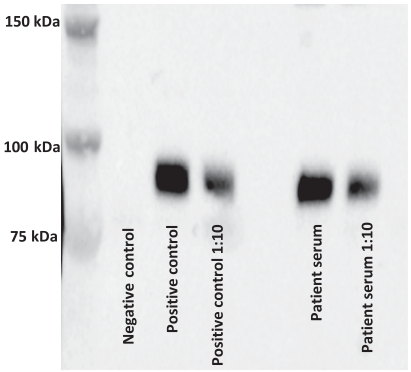


**FIGURE 3**
Immunoprecipitation semiquantitative assay for insulin receptor antibodies. The positive control was from a previous patient with a classic presentation and a strongly positive antibody result, and the negative control is healthy control serum.

receptor autoantibodies in high titers (Fig 3).

For the treatment of hypoglycemia, the patient was managed initially by frequent oral and enteral feeding, along with oral high-dose corticosteroids, mycophenolate mofetil, rituximab, intravenous immunoglobulin (IVIG), and plasmapheresis. The episodes of hypoglycemia decreased but continued, highlighting her poor response to B-cell immunomodulation. A novel immune therapy, bortezomib (Velcade), was initiated to control antibody-mediated hypoglycemia. Over the intervening months, the intensity of hypoglycemia decreased but has not completely resolved (Fig 4). The addition of CGM has provided the ability to monitor glucose trends and avert severe episodes of hypoglycemia.

## DISCUSSION

The antibodies in autoimmune hypoglycemia can be against the insulin peptide, known as insulin autoimmune syndrome, or insulin receptor antibodies in type B insulin resistance.[1] However, the predominance of signs of insulin resistance and hyperandrogenism, the concomitant presence of rheumatologic disease, and the poor response to therapy suggest type B insulin resistance. Although it can affect males and younger patients, it usually presents in middle-aged women.

Our pediatric patient had glucose abnormalities preceded by other autoimmune disorders. The presence of multiple autoimmune disorders places her in the category of autoimmune overlap syndrome (Table 1). Autoimmune overlap syndrome is defined as the presence of ≥2 autoimmune diseases in a patient, and this classification helps in defining management and understanding the prognosis of the patient.[4] Autoimmune diseases usually precede the metabolic problems of type B insulin resistance, with the most frequent underlying condition being SLE.[5]

### Pathophysiology

The presence of polyclonal antibodies against the insulin receptor is the hallmark of type B insulin resistance syndrome and is responsible for the abnormalities in glucose homeostasis. Physiologically, hypoglycemia tends to be associated with low titers of insulin receptor autoantibody, whereas high titers are associated with hyperglycemia.[6] These antibodies, when acting

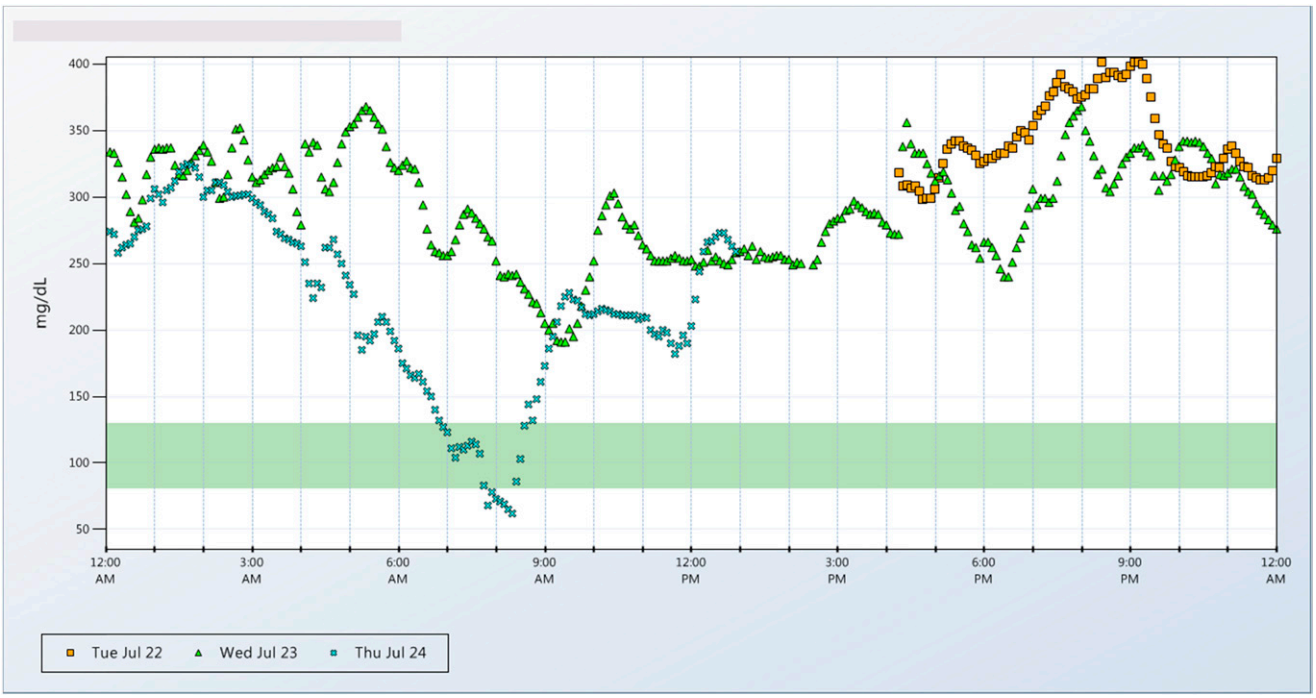


**FIGURE 4**
Continuous glucose monitoring shows blood glucose variability with hyper- and hypoglycemia.

**TABLE 2** Diagnostic Fasting Study During Hospital Admission

| Parameter | Patient Value | Normal Values and/or Interpretation |
|---|---|---|
| Baseline blood glucose | 153 mg/dL | 90–160 mg/dL |
| Blood glucose at 5 h fasting duration | 49 mg/dL | Fasting hypoglycemia defined as blood glucose <50 mg/dL |
| β hydroxybutyrate | 0.2 mmol/L | Suppressed serum ketones |
| Free fatty acid | 0.35 mmol/L | Suppressed free fatty acid |
| Insulin | 937.6 uIU/mL | Elevated insulin level |
| C-peptide | 7.1 ng/mL | Elevated C-peptide |
| Insulin/C-peptide molar ratio | 2.8 | <1 |
| Blood glucose after administration of intravenous glucagon | 109 mg/dL, blood glucose increased by 60 mg/dL from baseline | Positive glucagon stimulation test indicating insulin mediated hypoglycemia |

agonistically, can lead to activation of the downstream insulin signaling pathway and result in hypoglycemia. Hypoglycemia can then be followed by increased receptor degradation, a decreased number of cell-surface insulin receptors, with subsequent insulin resistance (antagonistic effect), and development of hyperglycemia.

Abnormalities in glucose homeostasis range from extreme insulin resistance and clinical diabetes to fasting hypoglycemia. In some cases, there can be a change from hyperglycemia to intractable hypoglycemia. In a long-standing series, Arioglu et al[6] reported that 24% of patients manifested some form of hypoglycemia during the course of their illness. The hypoglycemia may occur in the fasting or the postprandial state.

Acanthosis nigricans and hyperandrogenism, although commonly seen in these patients as a part of the insulin resistance picture, are not pathognomonic for this syndrome.[7] Ultrasonography may show ovarian cysts as a manifestation of insulin-mediated hyperandrogensism.[6] Our patient exhibited both of these features (Fig 2), although she did not have premature adrenarche. Hyperandrogenism and ovarian enlargement can remit with a decrease in insulin receptor antibody levels.[6]

## Evaluation

Diagnosis can be challenging. Our patient fulfilled the clinical definition of type 1 DM with classic symptoms of polyuria and polydipsia, hyperglycemia, and high titers of GAD-65 antibodies. Accordingly, she received treatment with subcutaneous insulin. However, her elevated insulin level of 937.6 uIU/mL (range: 1.7–55.9) and C-peptide level of 7.1 ng/mL (range: 0.8–3.5) were not consistent with the destruction of pancreatic β cells as seen in true type 1 DM. The presence of GAD-65 antibodies, similar to her thyroid antibody positivity in the face of normal thyroid function, is likely secondary to her overwhelming autoimmune state. Therefore, her initial misdiagnosis of type 1 DM had clouded her presentation of type B insulin resistance. Our case is complementary to a previously reported case of an obese 55-year-old male presenting with type 2 diabetes, without physical signs of insulin resistance, who was later found to have severe insulin resistance due to insulin-receptor antibodies.[8] Our pediatric patient was thought to have what was typical type 1 DM, with her diagnosis later evolving into classic type B insulin resistance syndrome, with alternating severe hyper- and hypoglycemia.[9]

Nonketotic hypoglycemia with a rise in BG level on glucagon challenge is the hallmark of insulin-mediated hypoglycemia. Insulin is produced and cosecreted in equimolar amounts with C-peptide; therefore, under normal circumstances, the molar ratio should be close to 1. Our patient had an elevated molar ratio, consistent with type B insulin resistance (Table 2). This phenomenon is related to impaired insulin degradation and poor insulin clearance due to a functional lack of insulin receptor.

Other laboratory findings include a paradoxical elevation of adiponectin.[10] This finding is postulated to be the result of loss of insulin action in adipocytes due to the loss of insulin receptor function.[11] Also, in contrast to other hyperglycemia and insulin-resistant states, patients with type B insulin resistance have surprisingly normal (relatively low compared with their insulin-resistant state) fasting triglyceride levels.[1]

## Management

Therapeutic interventions are divided into 2 categories: (1) therapy to achieve euglycemia, and (2) therapy to modulate the autoimmune response.[4] The hyperglycemic phase can usually be managed by high-dose insulin and/or oral agents. Treatment of hypoglycemia involves immunomodulatory therapies, such as a high dose of glucocorticoids, employed to control autoantibody production, and is usually guided by the protocols used to treat the underlying condition, such as lupus nephritis.[6]

Frequently, a combination of steroids and immunomodulators, such as azathioprine, rituximab, and cyclophosphamide, are used.[2] Alternative strategies include IVIG and plasma exchange. Our patient continued to have low blood sugar despite pulse steroids, cycles of IVIG, rituximab, and plasma exchange. She was then treated with bortezomib, a newer drug used in the treatment of multiple myeloma, which acts by

proteasome inhibition and increased apoptosis of antibody-producing cells.[3]

New technologies, such as CGM, add a dynamic facet to the management of type B insulin resistance. The ability to monitor glucose in real time provides a tool to avert severe hypoglycemia, especially in children who are not cognizant of neuroglycopenic symptoms or those with hypoglycemia unawareness. Upcoming advances in diabetes care, such as integrated insulin delivery systems (CGM combined with subcutaneous pump delivery of insulin and glucagon), may provide the capability to respond to both hyper- and hypoglycemia.[12]

### Prognosis

Although autoantibodies remit spontaneously in one-third of patients, the mortality rate of the disease continues to be high and appears to be primarily driven by the severity of the underlying disease. Both fasting hypoglycemia and a switch from hyperglycemia to hypoglycemia are indicators of poor prognosis and may lead to mortality due to intractable hypoglycemia.[6]

## CONCLUSIONS

DM is a common pediatric disease seen both by general pediatricians and subspecialists. Hypoglycemia, although common with insulin therapy, if severe, recurrent, or unexplained may indicate a more complex pathophysiology. Careful history and physical examination may promote timely diagnosis and treatment. This patient's presentation with a classic picture of type 1 DM added a layer of diagnostic dilemma before her final diagnosis of type B insulin resistance. The use of adjunct glucose monitoring devices and an enteral feeding regimen have provided additional tools to prevent severe hypoglycemic episodes.

### ABBREVIATIONS

BG: blood glucose
DM: diabetes mellitus
CGM: continuous glucose monitoring
IVIG: intravenous immunoglobulin
SLE: systemic lupus erythematosus

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*Pediatrics* 2017;139;
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