A Case of Persistent Hypoglycemia: When to Think Outside the Box

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PRESENTATION
A 71-year-old Chinese woman with autoimmune Hashimoto’s hypothyroidism and mixed connective tissue disease (MCTD) was referred to the Endocrine Unit for frequent episodes of hypoglycemia. The patient was diagnosed with diabetes by her general practitioner several weeks earlier and started on metformin for symptoms of polyuria, polydipsia, and a random blood glucose level of 468 mg/dl.

The hyperglycemia was initially thought to be secondary to initiation and subsequent increase in dose of the steroid used for treatment of her MCTD. A week after taking metformin, she noted increased episodes of palpitations, dizziness, and diaphoresis, which were relieved with food intake. She subsequently decided for herself to discontinue the metformin.

Her fasting capillary blood glucose readings were 44–55 mg/dl. Hypoglycemia occurred despite constant and pre-planned food intake. Additionally, these episodes of hypoglycemia became more frequent with discontinuation of her oral...
hydroxychloroquine (because of skin hyperpigmentation) and steroids, and the hypoglycemia persisted until she sought medical care.

During the patient’s inpatient workup for hypoglycemia, numerous fasting capillary blood glucose readings ranged from 32 to 65 mg/dl, and 2-hour postprandial glucose readings were between 47 and 61 mg/dl. These readings were confirmed with measurements of serum blood glucose. The patient’s A1C was 5.7%. Because of her frequent and persistent hypoglycemic events, she was given a continuous dextrose drip and advised to eat frequent meals.

Given her history of chronic steroid use, a low-dose adrenocorticotropic hormone stimulation test was performed to assess her hypothalamic-pituitary-adrenal axis; results were consistent with adrenal insufficiency. She was then placed on daily replacement doses of hydrocortisone, 10 mg every morning and 5 mg every evening. Despite having steroid replacement, taking frequent meals, and being on a 10% continuous dextrose drip, her hypoglycemia continued.

There was no history of insulin use. During inpatient monitoring, there was no evidence to suggest exogenous insulin or any medication that can contribute to hypoglycemia. Screening for plasma sulfonyleureas, biguanides, insulin analogs, and insulin antibodies were negative. Imaging of the abdomen and pancreas was normal.

Results of a 72-hour fast was consistent with hyperinsulinism (Table 1). Given the hyperinsulinism, underlying autoimmunity, and Asian ethnicity, as well as her history of insulin naivete, screening for insulin antibodies was performed, but none were detected. We subsequently measured insulin receptor antibodies, which confirmed their presence.

The patient was diagnosed with type B insulin resistance syndrome and restarted on prednisolone, 20 mg/day, and immunosuppressive therapy (azathioprine, 25 mg/day), resulting in decreased hypoglycemic episodes. She is now symptom free on oral prednisolone and azathioprine, 100 mg daily.

**QUESTIONS**
1. What are the causes of persistent hypoglycemia and when do we have to “think outside the box” to reach a diagnosis?
2. How do patients with type B insulin resistance typically present?
3. What is the underlying pathophysiology of type B insulin resistance?
4. What are the treatment options for this syndrome?

**COMMENTARY**
Autoimmune syndromes are rare causes of hypoglycemia. Interpretation of the standard tests used in evaluation of hypoglycemia may be confusing in these patients. The presence of type B insulin resistance needs to be considered in the setting of rheumatological conditions or with any autoimmune disease such as systemic sclerosis, systemic lupus erythematos (SLE), Hashimoto’s thyroiditis, or autoimmune thrombocytopenia. In type B insulin resistance, there is presence of polyclonal immunoglobulin G antibodies against the insulin receptor, resulting in hyperglycemia, hypoglycemia, or both.

In a case series describing the general features and natural history of type B insulin resistance of 24 patients followed at the National Institutes of Health for up to 28 years, SLE was the rheumatological disease most consistently associated with type B insulin resistance. Most patients also presented with clinical features consistent with acanthosis nigricans, with involvement of the periorcular and perioral areas, hyperandrogenism, and ovarian enlargement (in women).

In type B insulin resistance, resistant and persistent hyperglycemia requiring high doses of insulin is the most common initial presentation. Patients can also present with features of active autoimmune disease occurring concurrently or before the presentation of type B insulin resistance. Fasting hypoglycemia (with or without postprandial hyperglycemia) or hypoglycemia occurring during the course of their disease,

**Table 1. Patient’s Serum Parameters After a 72-Hour Fast**

<table>
<thead>
<tr>
<th>Serum Parameters</th>
<th>Normal Range</th>
<th>Patient’s Results</th>
</tr>
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<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>70–110</td>
<td>19.8</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>3.0–25.0</td>
<td>118.5</td>
</tr>
<tr>
<td>C-peptide (ng/ml)</td>
<td>0.9–4.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Proinsulin (µU/ml)</td>
<td>Fasting &lt; 0.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>8.3–13.9</td>
<td>56</td>
</tr>
<tr>
<td>Anti-insulin receptor antibodies</td>
<td>—</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-insulin antibody</td>
<td>—</td>
<td>Negative</td>
</tr>
<tr>
<td>Analog insulin</td>
<td>—</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*Results demonstrated hyperinsulinemia and elevated C-peptide and adiponectin levels in the setting of a serum glucose level in the hypoglycemic range. Anti-insulin receptor antibodies were present in patient’s serum. There was no evidence of analog insulin or anti-insulin antibodies in the circulation.
even subsequent to a period of hyperglycemia and diabetes,\textsuperscript{1,2} may occur. Isolated hypoglycemia, such as in this patient, is a much rarer presentation.\textsuperscript{3} Thus, the clinical course in type B insulin resistance can alternate between the hyper- and hypoglycemic states, making management of these patients particularly challenging.

It is still unclear if this patient’s single episode of documented hyperglycemia was related to her underlying type B insulin resistance. In our opinion, this is less likely given the fact that most cases of hyperglycemia in type B insulin resistance are resistant to therapy, and the hyperglycemia phase lasts much longer.

The presence of anti-insulin receptor antibodies are the diagnostic hallmark of the type B syndrome. It appears that anti-insulin receptor antibody titers are proportionate to the magnitude of insulin resistance.\textsuperscript{4} The presence of anti-insulin receptor antibodies may occur as a result of either loss of immune tolerance or generation of an immune response to an exogenous antigen and autoantibody formation through molecular mimicry.\textsuperscript{4}

Although the pathogenesis of type B insulin resistance remains largely undetermined, it is believed that the presence of antibodies against insulin receptors leads to insulin resistance by interfering with insulin binding.\textsuperscript{5} Depending on the antibody titer levels, a clinical picture of resistant hyperglycemia or hypoglycemia, or a fluctuation between the two states, can develop. It is postulated that, at high titers, these anti-insulin receptor antibodies become antagonistic to the insulin receptor and sterically inhibit insulin binding. This results in inhibition of physiological glucose transport, prevention of insulin clearance, and high levels of plasma insulin that are ineffective or insufficient to maintain normal blood glucose levels, resulting in hyperglycemia.

At low antibody titers, however, either spontaneously or from therapeutic measures such as plasma exchange or immunosuppressive drugs, hypoglycemia can occur as a result of antibody activation of the insulin receptor\textsuperscript{6} (i.e., these antibodies then act as agonists to the insulin receptor). In vitro studies of serum samples from patients with type B insulin resistance have demonstrated that the persistent hypoglycemia is the result of enhanced insulin binding.\textsuperscript{7}

Several laboratory findings are fairly consistent in type B insulin resistance syndrome. Hyperinsulinemia is a consistent finding.\textsuperscript{7} Possible mechanisms of hyperinsulinism include increased insulin secretion to compensate for the peripheral insulin resistance and, in many cases, reduced insulin clearance.\textsuperscript{8} Even when patients with type B insulin resistance present with hypoglycemia, hyperinsulinism that is inappropriate to the degree of hypoglycemia is usually seen. In familial forms of insulin receptor mutation leading to persistent hypoglycemia, the hyperinsulinism seen in the setting of hypoglycemia has been found to be the result of an impairment in insulin metabolism, more so than a result of insulin hyper-secretion.\textsuperscript{8}

Another laboratory finding that can aid in the diagnosis is the ratio of insulin to C-peptide level. In the setting of hypoglycemia in type B insulin resistance, there is a typical elevation in this ratio of $\sim 0.2–0.5$.\textsuperscript{8} The patient described here demonstrated an elevated ratio of insulin to C-peptide of 1.3 (done in molar comparison, insulin 823 pmol/l, C-peptide 615 pmol/l). Although the exact cause is unclear, a possible explanation for this finding may be a combination of insulin resistance and impaired insulin degradation and insulin clearance. Additionally, a component of insulin hypersecretion cannot be ruled out.

A paradoxical elevation of adiponectin in type B insulin resistance has also been reported. Adiponectin is a protein produced in adipose tissue, and its levels are usually low in insulin resistance. The rise in adiponectin in type B insulin resistance is presumed to be the result of direct effects on adipocytes of the loss in insulin receptor function or the result of loss of insulin action in mature adipose tissue.\textsuperscript{8} Adiponectin levels have been found to be quite helpful in the diagnosis of insulin receptor dysfunction in patients with type B insulin resistance. A level of 7 mg/l has a 97% positive predictive value and a level of 5 mg/l has a 97% negative predictive value.\textsuperscript{9}

Other laboratory findings associated with type B insulin resistance include elevated insulin-regulated hepatic proteins, sex hormone binding globulin, insulin-like growth factor binding protein 1, and decreased triglyceride levels.\textsuperscript{2} In contrast to other types of insulin resistance, in which hypertriglyceridemia tends to be present, patients with type B insulin resistance exhibit unusually low triglyceride levels.

Treatment of type B insulin resistance is targeted at decreasing the levels of circulating antibodies. High doses of glucocorticoids are usually used in an attempt to reverse the hypoglycemia.\textsuperscript{10–12} Current therapeutic strategies include various immunosuppressive agents, intravenous immunoglobulins, or plasma exchange; however, optimal regimens or combinations of regimens have not been established. Frequently, a combination of steroids and immunomodulators is used. One such combination...
includes high-dose steroid therapy and azathioprine, a regimen that was successful in this patient. In a recent report, the combined use of rituximab, cyclophosphamide, and pulse steroids resulted in remission of the disease.

**CLINICAL PEARLS**

- In patients with hyperinsulinemic hypoglycemia, especially in the setting of autoimmune or rheumatological disease, the diagnosis of type B insulin resistance syndrome needs to be considered.
- In this syndrome, insulin receptor antibodies are present and are either antagonistic or agonistic to the insulin receptor. Patients can present with hyperglycemia or hypoglycemia or may alternate between these glycemic states depending on their insulin receptor antibody titer levels.
- Although it is a rare condition, awareness of type B insulin resistance is essential to allow for proper management because treatment usually includes multimodal immunosuppression to target pathogenic antibodies and prevent unnecessary invasive procedures.

**REFERENCES**


Yogeswari Venugopal, MBBS, is an endocrinology fellow, Shirene Vethakkan, MBBS, is a senior lecturer, and Karen Choong, MD, is an associate professor in the Department of Endocrinology, Diabetes, and Metabolism; and Sargunan Sockalingam, MBBS, is associate professor, and Raja Jasmin, MBBS, is a medical lecturer in the Department of Rheumatology at the University of Malaya, Kuala Lumpur, Malaysia.