

## Clinical Vignettes

# Recurrent Hypoglycemia from Insulin Autoimmune Syndrome

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Insulin autoimmune syndrome (IAS) is an uncommon cause of hyperinsulinemic hypoglycemia characterized by autoantibodies to endogenous insulin in individuals without previous exposure to exogenous insulin. IAS is the third leading cause of spontaneous hypoglycemia in Japan, and is increasingly being recognized worldwide in non-Asian populations. We report a case of IAS in a Caucasian woman with recurrent complaints of hypoglycemia, with laboratory findings of serum glucose 2.5 mmol/L (45 mg/dL), insulin 54,930 pmol/L (7.909  $\mu$ IU/mL), connecting peptide (C-peptide) 4,104 pmol/L (12.4 ng/mL), and a corresponding insulin to C-peptide molar ratio of 13.4 during a spontaneous hypoglycemic event. Autoantibodies to insulin were markedly elevated at > 50 kU/L (> 50 U/mL). IAS should be considered in the differential diagnosis of hypoglycemia in non-diabetic individuals. Distinction from insulinoma is especially crucial to prevent unwarranted invasive procedures and surgical interventions in hypoglycemic patients.

**KEY WORDS:** insulin autoimmune syndrome; hypoglycemia; insulin to C-peptide molar ratio.

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## CASE REPORT

A 45-year-old Caucasian woman presented to clinic with a 6-week history of recurrent hypoglycemic symptoms consisting of fatigue, lightheadedness, blurry vision, and diaphoresis. The episodes were triggered by fasting and exercise, and alleviated with food intake. She also reported a 10-pound weight gain during this period. There was no history of diabetes mellitus in the patient or her family, and she had no access to insulin and/or insulin secretagogues. Past medical history was significant for endometriosis requiring multiple pelvic surgeries, von Willebrand disease, hepatic steatosis, gastroesophageal reflux disease, and

patellofemoral syndrome. The patient took esomeprazole occasionally but no other prescription or over-the-counter medications. She did not smoke, drink alcohol, or use recreational drugs. Family history was negative for any endocrine tumors or autoimmune diseases. Vital signs were normal and her physical examination was non-contributory.

Laboratory investigations revealed normal renal and liver function. Hemoglobin A1c was 5.4%. Adrenocorticotropic hormone (ACTH) stimulation test indicated an adequate cortisol response. Blood work was collected during a spontaneous symptomatic hypoglycemic event (Table 1). The markedly increased insulin level and the non-suppressed connecting peptide (C-peptide) result, along with the corresponding insulin to C-peptide molar ratio of 13.4, were incompatible with exogenous insulin administration as the cause of hypoglycemia.

Computed tomography (CT) of the abdomen did not identify any masses in the pancreas or in the retroperitoneum. Magnetic resonance imaging (MRI) of the abdomen was aborted due to feelings of claustrophobia in the patient. Selective arterial calcium stimulation was performed to differentiate between focal (e.g. insulinoma) and diffuse (e.g. islet cell hypertrophy) pancreatic pathologies, and to localize the source of hyperinsulinism. Regardless of the sampling site, all specimens had similarly raised insulin and C-peptide levels (Table 1).

Due to the magnitude of insulin elevation and the insulin to C-peptide molar ratio of > 1—which was physiologically impossible—an interference with the laboratory assay was suspected. However, pre-incubation of the patient's serum samples with heterophilic blocking tubes<sup>1</sup> did not alter the results. An autoimmune form of hypoglycemia was thereby considered, and autoantibodies to insulin were found to be markedly increased at > 50 kU/L (> 50 U/mL) (reference range: < 0.4 kU/L).

Workup for autoimmune diseases (including anti-nuclear antibodies and rheumatoid factor) and monoclonal gammopathy did not reveal any significant findings. The patient was advised to follow a low glycemic index diet with frequent small meals. The occurrence of hypoglycemic episodes decreased, but continued to manifest during exertion. Unfortunately, the patient did not tolerate acarbose and refused a trial of corticosteroids. Her most recent laboratory investigations demonstrated improved, but persistently raised, insulin

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**Table 1. Laboratory Investigations Performed in Our Patient with Insulin Autoimmune Syndrome (IAS)**

Analyte	Patient Result	Reference Range
During a spontaneous episode of symptomatic hypoglycemia		
Serum glucose	2.5 mmol/L (45 mg/dL)	3.6–7.8 mmol/L
$\beta$ -hydroxybutyrate	< 0.30 mmol/L (< 3.1 mg/dL)	< 0.30 mmol/L
Insulin	54,930 pmol/L (7,909 $\mu$ IU/mL)	< 10 pmol/L when glucose $\leq$ 2.7 mmol/L
C-peptide	4,104 pmol/L (12.4 ng/mL)	230–990 pmol/L
Insulin/C-peptide molar ratio	13.4	< 1
Selective arterial calcium stimulation test		
Insulin (all specimens)	> 34,000 pmol/L (> 4,895 $\mu$ IU/mL)	–
C-peptide (all specimens)	> 5,000 pmol/L (> 15 ng/mL)	–
Other laboratory test results		
Liver function	Unremarkable	–
Kidney function	Unremarkable	–
Hemoglobin A1c	5.4 %	4.8–6.2 %
ACTH stimulation test	Adequate cortisol response	–
Heterophile antibodies	Negative	–
Insulin autoantibodies	> 50 kU/L (> 50 U/mL)	< 0.4 kU/L
Rheumatoid factor	< 30 IU/mL	< 30 IU/mL
Antinuclear antibodies	Negative	–
Serum protein electrophoresis	No paraprotein detected	–

and C-peptide levels of 778 pmol/L (112  $\mu$ IU/mL) and 1,167 pmol/L (3.5 ng/mL) respectively.

## DISCUSSION

Insulin autoimmune syndrome (IAS), or Hirata disease, is a rare cause of hyperinsulinemic hypoglycemia characterized by autoantibodies to endogenous insulin in individuals without previous exposure to exogenous insulin.<sup>2</sup> First described by Hirata *et al.* in 1970,<sup>3</sup> it is the third leading cause of spontaneous hypoglycemia in Japan following insulinoma and extrapancreatic neoplasms.<sup>4</sup> Over 380 cases have been reported in the medical literature since,<sup>5</sup> with the majority (90 %) depicted in the Japanese population. Regardless, IAS is also recognized in other countries, including Europe and the United States (US).<sup>6</sup> A compilation of all IAS cases described in the US is shown in Table 2. IAS should be considered in any hypoglycemic patient, especially in those with a suspected insulinoma, so as to avoid any unnecessary, invasive and costly procedures and surgical interventions.

Patients with IAS usually present in adulthood (typically after age 40) with postprandial hypoglycemia, although fasting and exercise-induced hypoglycemia have also been described.<sup>6</sup> The disease shows no overall predilection to gender. Affected individuals may complain of marked neuroglycopenic symptoms of confusion and an altered level of consciousness, and may even be in a comatose state on initial presentation.<sup>7</sup> Autoimmune comorbidities—such as Graves' disease, systemic lupus erythematosus, and rheumatoid arthritis—and/or monoclonal gammopathy may be elicited on history.<sup>6</sup> About half of IAS patients report recent exposure to medications, with over 90 % of offending agents containing a sulfhydryl group.<sup>8</sup> Methimazole is the most commonly implicated drug; others include carbimazole, glutathione, tiopronin, tolbutamide, gold

thioglycose, interferon- $\alpha$ , captopril, diltiazem, hydralazine, procainamide, isoniazid, D-penicillamine, imipenem and penicillin G.<sup>6,7,9</sup> Alpha-lipoic acid, a popular health supplement for the treatment of diabetic neuropathy and obesity, has been linked to IAS in recent years.<sup>5</sup>

Although the precise mechanism for hypoglycemia in IAS is unknown, the most widely accepted hypothesis is a mismatch between blood glucose and free insulin concentration, secondary to the binding and release of secreted insulin by autoantibodies.<sup>7</sup> Following a meal or oral glucose load, glucose concentration in the bloodstream rises, providing a stimulus for insulin secretion. Autoantibodies bind to these insulin molecules, rendering them unavailable to exert their effects. The resultant hyperglycemia not only promotes further insulin release, but may also explain the increased hemoglobin A1c often seen in IAS patients.<sup>6</sup> As glucose concentration eventually falls, insulin secretion also subsides, and the total insulin level decreases. Insulin molecules spontaneously dissociate from the autoantibodies at this time, giving rise to a raised free insulin level inappropriate for the glucose concentration, evoking hypoglycemia.<sup>7</sup> Insulin autoantibodies with a high binding capacity and a low affinity are more likely to bring about hypoglycemic symptoms.<sup>10</sup> Medications containing a sulfhydryl group have been proposed to induce autoantibody formation by interacting with the disulfide bonds of the insulin molecule and augmenting its immunogenicity;<sup>11</sup> however, the true underlying pathophysiology remains unclear at this time. Rarely, the co-existence of both insulin autoantibodies and insulin receptor autoantibodies within the same patient has been described.<sup>12</sup>

A striking feature of IAS is the magnitude of insulin elevation—with results generally above 1,000 pmol/L<sup>13</sup>—secondary to the insulin assay reacting with the autoantibody-bound insulin molecules. Increased insulin level to this extent is rarely seen in insulinomas.<sup>7</sup> If free insulin levels are determined, they may be normal or raised. C-peptide and proinsulin concentrations

Table 2. Clinical Characteristics of Insulin Autoimmune Syndrome (IAS) Cases Reported in the United States

Patient	Age	Gender	Ethnicity	Associated Conditions/Medications	Reference
1	63	M	Caucasian	Multiple myeloma	18
2	16	M	African-American	Methimazole	19
3	67	M	Caucasian	Chronic myelomonocytic leukemia	6
4	71	M	Caucasian	—	6
5	80	F	—	—	20
6	73	F	Caucasian	Systemic lupus erythematosus	21
7	61	M	Caucasian	Ulcerative colitis	21
8	46	F	Caucasian	—	21
9	64	F	Caucasian	—	21
10	84	F	Caucasian	—	21
11	75	F	Caucasian	Propylthiouracil	21
12	72	F	Caucasian	—	21
13	77	M	Caucasian	—	22
14	55	M	Caucasian	Alcoholic cirrhosis, acquired inhibitors to factor V	23
15	74	M	African-American	Hydralazine	24
16	73	M	—	Multiple myeloma	25
17	52	F	Caucasian	Rheumatoid arthritis, penicillamine	26
18	33	M	Caucasian	Rheumatoid arthritis, penicillamine	26
19	61	F	Caucasian	Rheumatoid arthritis, penicillamine	11
20	82	F	Caucasian	Drug-induced lupus erythematosus (hydralazine, procainamide)	27
21	58	F	Caucasian	Rheumatoid arthritis	28
22	43	F	Latin-American (Honduran)	—	28
23	10 month	M	—	—	28
24	26	F	Caucasian	Pregnancy	28
25	48	F	Caucasian	—	28

are increased, and autoantibody titers indicate a high percentage of binding to insulin.<sup>6</sup> Hyperplasia of islet  $\beta$ -cells is observed on histological studies.<sup>11</sup>

Immunoassays are commonly used for the analysis of various hormones, including insulin. Although robust, immunoassays are subjected to interference from endogenous anti-reagent antibodies found in the serum of certain individuals. These antibodies, known as human anti-animal antibodies and heterophile antibodies, may bind to animal immunoglobulins in the assay and produce falsely high or low results.<sup>1,14</sup> A method to confirm the presence of anti-reagent antibodies is to treat the patient sample in question with heterophilic antibody blocking tubes; a significant difference in hormone level pre-incubation and post-incubation supports the presence of anti-reagent antibodies, and helps differentiate such antibodies from anti-analyte antibodies (e.g. insulin autoantibodies).<sup>1,14</sup>

C-peptide and insulin are co-secreted from pancreatic  $\beta$ -cells into the portal circulation in equimolar proportions. Whereas

insulin is principally cleared by the liver, C-peptide is mainly metabolized by the kidneys at a substantially slower rate, resulting in a difference in circulating half-life of 5–10 minutes versus 30–35 minutes, respectively.<sup>15</sup> Thus, despite equimolar secretion, the insulin to C-peptide molar ratio is normally  $< 1$ . The ratio may be reversed to  $> 1$  in two settings: the first is IAS, as demonstrated by our patient; the second is factitious hypoglycemia from exogenous insulin administration, in which insulin concentration is raised with a suppressed C-peptide level.<sup>15</sup> It is important to note that different commercial insulin assays exhibit variable cross-reactivities with synthetic insulin analogues.<sup>16</sup> Any dialogue regarding the cross-reactivity of the laboratory's insulin method is best initiated with the local clinical laboratory staff. Expected patterns of insulin, C-peptide, and insulin to C-peptide molar ratio for different causes of hypoglycemia are summarized in Table 3.

In 80 % of patients, IAS is a transient condition with spontaneous resolution within 3–6 months of diagnosis.<sup>17</sup> For those with intractable hypoglycemia, small frequent meals low

Table 3. Expected Patterns of Insulin, C-peptide, and Insulin to C-peptide Molar Ratio (During a Symptomatic Hypoglycemic Event) for Different Etiologies of Hypoglycemia

	Insulin	C-Peptide	Insulin/C-Peptide Molar Ratio	Other Findings
Insulin autoimmune syndrome	↑	↑	$> 1$	<ul style="list-style-type: none"> <li>• Presence of insulin autoantibodies in blood</li> <li>• Localization of insulinoma on imaging and/or on selective arterial calcium stimulation study</li> </ul>
Insulinoma	↑	↑	$< 1$	
Exogenous insulin administration	↑	Suppressed	$> 1$	<ul style="list-style-type: none"> <li>• Access to insulin may be elicited on history</li> <li>• Potentially discordant insulin results from different insulin assays due to variable method cross-reactivities with synthetic insulin analogues</li> <li>• Access to insulin secretagogues may be elicited on history</li> <li>• Detection of sulfonylureas or meglitinides in blood or urine</li> </ul>
Insulin secretagogue intoxication	↑	↑	$< 1$	

in carbohydrates remain the first line of treatment; the rationale for this is to avoid postprandial hyperglycemia, and thereby the stimulus for insulin secretion.<sup>7</sup> Glucocorticoid therapy (e.g. oral prednisone 30–60 mg/day) may be useful as an adjunct therapy.<sup>7</sup> Any potentially incriminating medication should be discontinued. Other therapeutic options, such as acarbose (to decrease carbohydrate digestion and absorption), diazoxide, octreotide and partial pancreatectomy (to restrict insulin release), and plasmapheresis (to reduce insulin autoantibody titers) have demonstrated varying success in the management of IAS.<sup>6</sup>

## CONCLUSION

IAS should be considered in any patient undergoing evaluation for hypoglycemia. Discrepancies between an unusually high insulin concentration and only moderately raised proinsulin and C-peptide levels, with a concurrent insulin to C-peptide molar ratio of  $> 1$ , are suggestive of IAS. Involving local laboratory physicians in the workup for IAS, especially in the exclusion of spurious insulin results from heterophilic interference, is strongly encouraged. Misdiagnosis may lead to unwarranted and inappropriate patient therapy, with considerable implications for clinical care.

## KEY POINTS

1. Insulin autoimmune syndrome (IAS) is an uncommon and mostly transient condition that should be considered in the differential diagnosis of hypoglycemia in non-diabetic patients.
2. Laboratory investigations suggestive of IAS include a significantly elevated insulin level, an increased C-peptide concentration, and an insulin to C-peptide molar ratio of  $> 1$ .
3. A detailed drug history should be taken, and co-existing autoimmune disorders and/or monoclonal gammopathy sought, although these are not required for the diagnosis of IAS.

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