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Case Report

Severe hypoglycemia secondary to methimazole-induced insulin autoimmune syndrome in a 16 year old African-American male

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Insulin autoimmune syndrome (IAS) or Hirata's disease is a rare disorder characterized by hypoglycemia secondary to insulin autoantibodies (IAb). Over 200 patients have been described from Japan with significantly less numbers being reported from outside the Orient. IAS is more common in patients older than 40 yr of age with reports in the pediatric age group being notably rarer. Exposure to sulfhydryl group containing medications is implicated in the pathogenesis of this syndrome. In this report, we describe a case of IAS in an African-American adolescent. A 16-yr-old healthy African-American male was diagnosed with Graves' disease and started on Methimazole. Four weeks later, he was found unconscious and hypoglycemic (blood sugar 1.5 mmol/L). Evaluation was negative for insulinoma. Insulin antibodies were positive. Oral glucose tolerance test revealed elevated free insulin concentrations with disproportionately elevated total insulin levels. The patient was started on prednisone, diazoxide, and propranolol for management of IAS and hyperthyroidism. Thyroid radio-ablation was subsequently undertaken. The doses of prednisone and diazoxide were tapered and these medications discontinued after 9 months. The insulin antibody levels decreased gradually and became undetectable in 6 months with resolution of the hypoglycemia.

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Insulin autoimmune syndrome (IAS), or Hirata's disease, is a rare disorder characterized by hypoglycemia associated with insulin autoantibodies (IAb) in serum (1). The first case report of IAS was documented by Hirata in 1970 (2). IAS is the third leading cause of hypoglycemia in Japan with over 200 cases being reported (3). The incidence outside the Orient is significantly less (1). The peak onset of this condition is 60–69 yr of age (4). Reports of this disorder in African-Americans and in children are distinctly rare (1).

IAS is characterized by fasting and/or postprandial hypoglycemia, high serum concentrations of total

immunoreactive insulin, and presence of serum polyclonal autoantibodies against insulin (2). It has been strongly related with previous exposure to sulfhydryl group containing medications, such as Methimazole (MTZ), as well as to alpha lipoic acid (3, 6, 10, 11, 12). The proposed mechanism of IAS is that binding of insulin to the antibodies reduces the availability of the secreted insulin, resulting in hyperglycemia and further insulin secretion; once blood glucose concentration begins to decrease and endogenous insulin secretion declines, the unregulated release of insulin bound to the antibodies results in inappropriately high concentration of free insulin and ensuing hypoglycemia (1). Furthermore, studies suggest that insulin presented by HLA class II molecules coded by DRBI*0406, DQAI*0301, and/or DQB 1 *0302 induces T-lymphocyte proliferation in IAS (5), suggesting that certain populations are at higher risk. In the current report, we describe a rare case of a MTZ-associated IAS in an African-American adolescent.

Case report

A healthy 16-year-old African-American male was diagnosed with Graves' disease in summer 2010. At diagnosis thyroid stimulating hormone level was <0.01 mU/L (reference range: 0.3–5.5 mU/L), Free T4 was 72 pmol/L (5.6 ng/dL, reference range: 0.9–1.8 ng/dL), and total T3 was 7.9 nmol/L (514 ng/dL, reference range: 60–181 ng/dL). In August 2010, he was started on MTZ 20 mg three times a day (TID) and propranolol 10 mg TID. Four weeks after starting MTZ, the patient experienced drowsiness and fell asleep in the classroom. The following morning, he was found unresponsive in his dormitory room. Emergency medical service measured the blood sugar level to be 1.5 mmol/L (27 mg/dL) and the patient was treated with D50 bolus. Patient was transported to a local emergency department. Upon arrival, he presented with seizure and blood sugar level was 2.6 mmol/L (48 mg/dL). He was administered a second bolus of D50 and was subsequently intubated for airway protection. He received supplemental dextrose for continued hypoglycemia, and was monitored in the intensive care unit. Physical examination did not reveal acanthosis nigricans and he was not obese (BMI 24 kg/m^2). Evaluation upon admission was significant with abnormal thyroid function tests consistent with active Graves' hyperthyroidism, and elevated C-peptide and insulin levels suggestive of endogenous hyperinsulinism. Laboratory tests to evaluate for an infectious process, drug abuse, exogenous insulin, and multiple endocrine neoplasias were unremarkable (Table 1). Brain MRI was negative for masses or hemorrhage.

At day 4 of presentation, repeated laboratory tests for evaluation of hyperinsulinism was significant for a high C-peptide level of 3.34 nmol/L (reference range: 0.3–1.3 nmol/L) and high insulin level of 1184.5 pmol/L (reference range: 21.5–200.9 pmol/L). Glucose level at that time, however, was 16.3 mmol/L (295 mg/dL). The patient required D7.5–D10% in IV fluids to maintain euglycemia. A trial of IV fluids without dextrose was attempted; the blood glucose dropped from 3.94 mmol/L (71 mg/dL) to 2.6 mmol/L (48 mg/dL) within 12 min of discontinuation of dextrose. Given the concern for IAS, Propylthiouracil (PTU) was substituted for MTZ. Liver function tests were monitored during his hospital stay and were unremarkable. Abdominal ultrasound was negative for tumor.

In addition to regular food intake, the patient required IV infusion of D7.5–12% (GIR =

Table 1. Baseline endocrine profile

	Laboratory test	Result	Reference range
Thyroid	TSH	0.01	0.30–5.50 mIU/L
	Free T4	28.7	9.7–21.8 pmol/L
	Free T3	0.123	0.029–0.060 pmol/L
	Total T3	4.6	1.23–2.69 pmol/L
	Thyroid receptor antibodies	12	0.00–1.75 IU/L
	Thyroid stimulating IG	1.5	<1.3
Adrenal	Cortisol (04:00 hours)	154.4	193.1–606.8 nmol/L
	ACTH	8.2	1.1–11.5 pmol/L
Parathyroid	Intact parathyroid hormone	2.21	1.05–6.84 pmol/L
	Total calcium	2.09	2.14–2.54 mmol/L
Pancreatic β-cell	Insulin	438	7.175–150.6 pmol/L
	C-peptide	3.8	0.33–1.7 nmol/L
	Hemoglobin A1C	5.8	3.8–6.4%
Tumor markers	Prolactin	7	3–23 μg/L
	BHCG	<2	<5 U/L
	Gastrin	35.4	25.0–111.0 ng/L

Table 2. Insulin antibody levels on three consecutive days

	Day 7 of presentation	Day 8 of presentation	Day 9 of presentation
Insulin antibody (Ref 0.00–0.02 nmol/L)	5.7	5.3	3.8

Insulin antibody (reference range: 0.00–0.02 nmol/L) was measured by at the Mayo Clinic (MN).

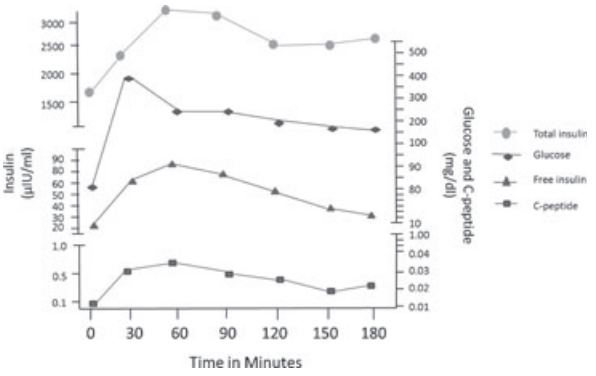

Fig. 1. OGTT results.

1.9–4.1 mg/kg/min) to avoid hypoglycemia with blood sugar levels ranging from 3.8 to 21.3 mmol/L (69–385 mg/dL). Computerized-tomography with optimized pancreas protocol was unremarkable. An Octreotide scan showed no scintigraphic evidence of insulinoma.

Insulin antibodies were evaluated due to suspicion of IAS. Insulin antibodies obtained on day 4 of presentation were significantly elevated at >50 unit/mL (reference range: <0.4 unit/mL). Insulin antibodies measured on days 7, 8, and 9 of presentation continued to be significantly elevated (Table 2).

To further evaluate the relationship between the serum concentrations of free insulin, total insulin, glucose, and C-peptide levels, the patient underwent an oral glucose tolerance test. A 75 g glucose load was given to the patient and blood samples were obtained every 30 min. The results of OGTT show that both free and total insulin levels were significantly elevated at all-time points (Fig. 1). Free insulin levels showed a slight increase at 30 min. C-peptide level was also raised at 30 min, but began to decline significantly by 90 min. Total insulin level increased markedly at 30 min, and declined slowly thereafter, but remained elevated above baseline, suggesting a delay in the clearance of total insulin.

Propranolol was used for the temporary control of his tachycardia. Persistent hypoglycemia was managed with prednisone and diazoxide. The patient underwent thyroid radio-ablation therapy. Six months later, IAB levels decreased to normal levels (0.01 nmol/L) and the medications were gradually weaned. The hypoglycemia has not recurred and he continues to receive levothyroxine replacement therapy for iatrogenic hypothyroidism.

Discussion

IAS is a rare cause of hypoglycemia which has been described mainly in the adult population with the majority of cases being reported from Japan (7). The current report highlights the possibility of this syndrome occurring in children and in African-Americans. The cause of IAS is not completely understood. Autoimmune disorders, previous exposure to alpha lipoic acid or sulfhydryl medications (such as MTZ), and certain HLA types have been implicated in the etiology of this syndrome. It has been hypothesized that sulfhydryl group drugs may cleave the disulfide bond of insulin molecule *in vivo* and enhance its immunogenicity (11). In some cases discontinuing sulfhydryl medication was found to correlate with remission, while re-introducing it was associated with recurrence of hypoglycemia (1). However, *in vitro* experiments involving incubation of insulin with sulfhydryl group drugs failed to demonstrate an effect on the insulin structure or immunoreactivity (1, 12). In our patient, the history of exposure to MTZ supports an etiological role for drugs with sulfhydryl group drugs in the development of IAS.

A striking feature of this patient's presentation was the extremely high levels of circulating insulin. This degree of elevated insulin in a patient with hypoglycemia would be suggestive of circumstances such as iatrogenic administration of insulin, insulinoma, or autoimmune syndromes including IAS and anti-insulin receptor antibodies (type B insulin resistance syndrome). Although insulin receptor antibodies were not measured, type B insulin resistance is unlikely. Rare cases of patients presenting with both insulin and insulin receptor antibodies have been reported (13); however, no new cases have been seen since the introduction of human insulin (1).

In IAS total insulin levels are markedly elevated, usually above 100 µU/mL (717.5 pmol/L) (1). In order to evaluate free and total insulin levels, 3-h OGTT was performed. Total insulin levels (free + bound insulin) were significantly elevated at all time points (Fig. 1). These increased markedly at 30 min, and declined slowly thereafter, but remained elevated above baseline. Free insulin levels showed a slight increase at 30 min and a slight decline after 90 min. The persistent elevation and slow decline of the total insulin levels as well as the elevated levels of serum insulin antibodies are consistent with IAS. The insulin antibodies done on day 4 of presentation were measured to Specialty Laboratories. The insulin antibodies obtained on days 7, 8, and 9 of presentation were measured to

Mayo Clinic Laboratory. Both laboratories used the radioimmunoassay method, although reference ranges are different.

Our patient was started on prednisone on day 7 of presentation and diazoxide on day 13 of presentation for suspected IAS. The potential benefits of prednisone included (i) elevation of blood sugar via insulin resistance; (ii) suppression of autoimmunity; and (iii) inhibition of conversion of T4 to T3. Stabilization of blood glucose levels was observed concurrently with discontinuation of MTZ and initiation of prednisone therapy. Further improvement in blood glucose without recurrence of hypoglycemia occurred once diazoxide was started. The mechanism for IAS resolution is unclear, but could be related to many factors including discontinuation of MTZ, initiation of prednisone therapy, and natural course of the disease.

This patient presented with minimally low cortisol level with normal ACTH level on day 7 of presentation (Table 1), although cortisol level was normal on day 1 of presentation (413.85 nmol/L, reference range: 118.6–623.5). Low cortisol level in the presence of hypoglycemia could be seen in patients with Addison's disease. However, since the ACTH level was not elevated and there was absence of overt signs such as mucosa hyperpigmentation to suggest Addison's disease, we judged this possibility to be very unlikely. His low cortisol level was more likely due to inadequate sleep because of the hospital setting or hyperthyroidism (14). Morning cortisol level 4 weeks after discontinuing prednisone therapy was within the normal range (331 nmol/L, reference range: 118.6–626.2 nmol/L).

Propranolol was started on inpatient day 17 due to tachycardia and systolic hypertension (blood pressure ranging 131-139/67-73). Although using propranolol in the presence of hypoglycemia can be risky because of its masking effect in the sympathetic response to hypoglycemia (15), remission of hypoglycemia had occurred 5 d prior to starting propranolol. He monitored his blood glucose four times a day and he did not experience any recurrent hypoglycemia. Propranolol was discontinued after thyroid ablation therapy.

In summary, we report a rare case of IAS in an African-American adolescent. IAS should be considered in the differential diagnosis of hypoglycemia in children who have had recent exposure to sulfhydryl group containing medications.

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