Case Report

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Insulin Autoimmune Syndrome – An After-Meal Roller Coaster Ride

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Abstract

Hypoglycemic disorders are rare in persons without diabetes, and clinical evaluation to identify its etiology can be challenging. We present a case of insulin autoimmune syndrome induced by carbimazole in a middle-aged Chinese man with underlying Graves' disease, which was managed conservatively with a combination of dietary modification and alpha-glucosidase inhibitor.

Key words: hypoglycemia, endogenous hyperinsulinism, insulin antibodies

INTRODUCTION

Hypoglycemic disorders are rare in persons without diabetes, and clinical evaluation to identify its etiology can be challenging. In a seemingly well individual, the differential diagnosis of hyperinsulinemic hypoglycemic disorders involves two main categories: Accidental, surreptitious or even malicious hypoglycemia and endogenous hyperinsulinism.[1] The causes of endogenous hyperinsulinemic hypoglycemia include insulinoma, post-bariatric hypoglycemia, nesidioblastosis, and insulin autoimmune syndrome.[2] We present an uncommon case of insulin autoimmune syndrome induced by carbimazole in a middle-aged Chinese man with underlying Graves' disease, which was managed conservatively with a combination of dietary modification and alpha-glucosidase inhibitor.

CASE

A 57-year-old Chinese male was brought to the emergency department for syncope. He experienced palpitations, sweating and hand tremors before he passed out a few hours after finishing his meal. He denied chest pain or shortness of breath. There was no history of tongue biting or urinary incontinence. He had no fever or altered bowel habits. He reported unintentional weight loss of 5 kg in 2 months. His medical history was notable only for hyperthyroidism. He was prescribed carbimazole by a general practitioner. However, he took the medicine irregularly. He smoked and drank alcohol occasionally. He did not consume traditional remedies or recreational drugs. There was no family history of diabetes mellitus or malignancy. His sister also had a thyroid disorder.

His capillary blood glucose on arrival was 2.6 mmol/L. He regained consciousness promptly after being given intravenous glucose. His vital signs remained within normal limits. He did not appear septic or cachexic. He had no Cushingoid features or skin hyperpigmentation. Systemic examination was otherwise unremarkable.

In the ward, he continued having recurrent symptomatic hypoglycemia, which happened either a few hours after food intake or during the fasting state, with capillary blood glucose levels ranging between 2.3 and 2.4 mmol/L. He required an intravenous 10% glucose infusion and was prescribed frequent, small portions of a complex carbohydrate diet.

Upon further questioning, the patient recollected similar symptoms had occurred several times prior to this event. His symptoms could either happen a few hours after eating food or during an empty stomach.

His complete blood count, renal and liver function were within the normal range. Glycated hemoglobin was 5.8%. Thyroid-stimulating hormone (TSH) level was 0.01 mU/L [Normal value (NV): 0.48 – 4.17 mU/L] with free thyroxine (T4) level of 12.2 pmol/L (NV: 10.7 – 18.4 pmol/L). He had elevated thyroid autoantibodies with anti-thyroid stimulating hormone receptor (TSH) antibody level of 21.88 IU/L (NV: < 1.75 IU/L) and anti-thyroid peroxidase antibody (TPO) of 9870.78 IU/mL (NV: 0 – 9 IU/mL). Tumour markers were not detected. A short corticotropin stimulation test was performed and the result showed an adequate response with a peak cortisol level of 860.3 nmol/L at 60 minutes. A prolonged fasting test was arranged however it was terminated prematurely due to the patient's non-

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Table 1. Results of prolonged Oral Glucose Tolerance Test

Time (Hour)	Random plasma glucose (mmol/L)	Insulin (pmol/L) (NV: 17.8 – 173)	C-Peptide (pmol/L) (NV: 367 – 1467)
0	2.4	>6945	2506
1	9.7	>6945	4298
2	14.4	>6945	5763
3	13.6	>6945	5755
4	6.3	>6945	4773
5	1.5	>6945	3538
6	1.5	>6945	3212

adherence. A prolonged oral glucose tolerance test (OGTT) confirmed endogenous hyperinsulinemic hypoglycemia (Table 1). Serum β-hydroxybutyrate was not raised. Plasma proinsulin and blood for sulfonylurea were not offered by our laboratory. Computed tomography of the pancreas showed no pancreatic mass.

With the combination of dietary adjustment and commencement of acarbose 50 mg thrice daily, we managed to stabilize his plasma glucose. He was discharged well after 2 weeks of admission. Advice on dietary and medication adherence was re-emphasized, together with regular self-monitoring of blood sugar.

As the assay was not widely accessible, serum insulin autoantibody (IA) titer was only measured 6 months after his initial presentation. Serum IA titer was measured on a chemiluminescent immunoassay platform. The first IA measurement recorded high levels of 113.9 IU/mL (NV: <20.0 IU/mL), indicating the presence of IA in a non-diabetic patient without exposure to exogenous insulin. Carbimazole was restarted at a lower dose when the outpatient review of the thyroid function test revealed an elevated free thyroxine (T4) level of 39.4 pmol/L with a thyroid stimulating hormone (TSH) level of 0.01 mU/L. Repeat measurement of anti-TSH receptor antibody titer at 11 months after carbimazole treatment showed a reduction from 21.88 IU/L to 4.15 IU/L. His second measurement of serum IA titer also declined from 113.9 IU/mL to 88.51 IU/mL, as reflected by no new episodes of hypoglycemia while receiving carbimazole treatment.

DISCUSSION

Establishing Whipple's triad, which entails a low plasma glucose level (less than 3.0 mmol/L), the associated symptoms, and the resolution of symptoms after correction of the glucose level, forms the cornerstone in managing a subject with a hypoglycemic disorder.[1,3] Insulinoma was initially suspected as the cause of our patient's symptoms. Nonetheless, he had clinical clues that were atypical for insulinoma, including a history of weight loss, postprandial symptoms, and an extremely high insulin concentration above 1000 pmol/L, which is unusual for insulinoma or beta-cell hypertrophy.[3,4]

According to the Endocrine Society guideline published in 2009, insulin antibodies should be screened when endogenous hyperinsulinism is confirmed by plasma glucose of less than 3 mmol/L, serum insulin of at least 18 pmol/L, C-peptide of at least 200 pmol/L, and β-hydroxybutyrate of less than 2.7 mmol/L.[1] Yukimasa Hirata and colleagues first described Insulin autoimmune syndrome (IAS) or Hirata's disease in 1970, and it is now recognized as the third most common cause of spontaneous hypoglycemia in Japan following insulinoma and non-pancreatic neoplasia.[3] IAS is usually seen in adult patients older than age 40 years of age with equal gender distribution. It is characterized by autoimmune antibodies to endogenous insulin in individuals without previous exposure to exogenous insulin.[5]

IAS can present as recurrent fasting hypoglycemia, alternating with postprandial hyperglycemia.[6] This distinctive clinical picture had been conveniently demonstrated by the findings from our prolonged OGTT. The exact pathophysiology of hypoglycemia in IAS is unclear. It is hypothesized that there is an altered kinetics of insulin clearance, due to "buffering" by autoantibodies, which sequester insulin in immune complexes during the acute phase of insulin secretion, only to release it slowly later, at physiologically inappropriate times.[6] When insulin autoantibodies bind to insulin, the half-life of insulin becomes prolonged from minutes to hours, while the half-life of the C-peptide remains unaffected. This phenomenon leads to disproportionately elevated plasma insulin levels while having a non-elevated plasma C-peptide which skewed the insulin to C-peptide molar ratio to more than 1.[7] In our patient, the insulin to C-peptide ratio throughout the prolonged OGTT ranged from 1.2 to 2.7.

Insulin autoantibodies are typically polyclonal in origin and are mostly of the immunoglobulin G class. They can be of high affinity with low binding capacity or low affinity with high binding capacity. The latter is often associated with clinical manifestations. These antibodies are virtually indistinguishable from the antibodies seen in up to 70% of children with type 1 diabetes.[8]

The prevalence of IAS varies according to race. The presence of HLA DR4 allele has been demonstrated in 96% of Japanese patients with IAS, indicating a susceptible genetic background in this syndrome.[3,5] In the past decade, the number of reported cases among Whites has also increased.[4] IAS is also known to be associated with hematological disorders or autoimmune diseases.[3,5] On the other hand, insulin autoantibodies may be triggered by medications, or exposure to viruses or they may manifest spontaneously (Table 2).[3,5,7]

The list of medications associated with IAS is extensive. The interaction of drugs containing the sulfhydryl group with the disulfide bond in the insulin molecule has been postulated to play a role. Antithyroid drugs such as methimazole and supplements such as alpha-lipoic acid are the most frequently prescribed medicines associated with IAS, followed by other groups of medication.[3,5,7] The

Table 2. Trigger factors and diseases associated with Insulin Autoimmune Syndrome[3,4,7]

Trigger Factors and Associated Diseases	Examples
Genetic predisposition	HLA-DR4
Autoimmune disorders	Graves' disease, rheumatoid arthritis, systemic lupus erythematosus
Hematological disorders	Multiple myeloma, monoclonal gammopathy of undetermined significance
Medications	
Antithyroid drugs	Methimazole, carbimazole, propylthiouracil
Supplements	Alpha-lipoic acid, glutathione
Antihypertensives	Captopril, hydralazine, procainamide
Antiplatelet drugs	Clopidogrel
Antibiotics	Penicillamine, imipenem, isoniazid
Anti-inflammatory drugs	Steroids, diclofenac
Proton pump inhibitors	Pantoprazole, omeprazole
Plasma proteins	Albumin
Viruses	Measles virus, mumps virus, rubella virus, varicella zoster virus, coxsackie B virus, hepatitis C virus

onset time of drug-induced IAS differs greatly, from days to months and even years after the drug exposure. On average, the onset time is 4 to 6 weeks.[7] IAS is usually a transient condition in Japanese patients, with spontaneous resolution of up to 80% within 3 to 6 months of diagnosis reported.[4,11] Meanwhile, in non-Asian patients, symptoms generally improve, and resolve completely over time if patients stop taking the drug that caused the symptoms.[5] Then again, there are scattered case reports and series which highlight that persistent recurrent hypoglycemia in IAS can last for years.[6,7]

At present, there are no guidelines available for the management of IAS. Trial of dietary modification is routinely advocated as the first line of treatment, followed by pharmacological interventions in those who fail to respond.[3-6] After the withdrawal of the culprit drug, the dietary recommendations include eating small frequent meals, avoiding simple carbohydrates, and a high-fiber diet. The rationale for this approach is to prevent postprandial hyperglycemia. Glycemic excursions after meals determine the amount of insulin released from the beta cells; the higher the excursion, the greater the insulin secreted and bound to the antibodies for future release.[9,10]

In our patient, due to limited drug access and safety concerns, we adopted a combination of dietary adjustment and acarbose to curb persistent hypoglycemia. Acarbose acts by inhibiting the membrane-bound intestinal alpha-glucosidase which hydrolyzes oligosaccharides, tri-saccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. This intervention staggers the glucose absorption and the postprandial glycemic excursions, thus reducing the quantum of insulin synthesis and secretion from the pancreatic β cells.[9] Other available drug therapies that can help to reduce pancreatic insulin secretion include somatostatin analogues and diazoxide.

Besides targeting endogenous insulin production, immune-modulating agents such as glucocorticoids, azathioprine, and rituximab have been used to decrease insulin autoantibodies levels.[3,5,9] In refractory cases, plasmapheresis or even pancreatic surgery have been tried by some investigators, with varying degrees of therapeutic success.[2,4,9-11]

Based on the literature review, IAS is largely a benign and self-limiting disorder. The recurrence rate of IAS after its full resolution is low.[3,5] Disease recurrence owing to the re-administration of the culprit drug only happens in a minority of patients. Our patient did not experience new hypoglycemic events when carbimazole was restarted at a lower dose. His insulin autoantibody titer also declined following the reduction of anti-TSH receptor antibody with carbimazole treatment.

CONCLUSION

In summary, our case highlights the importance of a structured diagnostic approach to spontaneous hypoglycemia. High insulin concentration along with insulin/c-peptide molar ratio of more than 1 should raise the clinical suspicion of IAS and is confirmed by the presence of high-titer insulin autoantibodies. Early recognition of this syndrome can avoid the need for laborious and costly investigations of presumed insulinoma.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CKL: Writing - original draft preparation; **HCW:** Writing - review and editing; **SA:** Writing - review and editing; **SLY:** Writing - review and editing

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References
1. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94(3):709-28. PMID: 19088155. https://doi.org/10.1210/jc.2008-1410.
2. Kittah NE, Vella A. Management of endocrine disease: Pathogenesis and management of hypoglycemia. Eur J Endocrinol. 2017;177(1): R37-47. PMID: 28381450. https://doi.org/10.1530/EJE-16-1062.
3. Cappellani D, Macchia E, Falorni A, Marchetti P. Insulin autoimmune syndrome (Hirata Disease): A comprehensive review fifty years after its first description. Diabetes Metab Syndr Obes. 2020;13:963-78. PMID: 32308449. PMCID: PMC7136665. https://doi.org/ 10.2147/DMSO.S219438.
4. Haverkamp GLG, Ijzerman RG, Kooter J, Krul-Poel YHM. The after-dinner dip. N Engl J Med. 2022;386(22):2130-6. PMID: 35648706. https://doi.org/10.1056/NEJMcps2106883.
5. Censi S, Mian C, Betterle C. Insulin autoimmune syndrome: From diagnosis to clinical management. Ann Transl Med. 2018;6(17):335. PMID: 30306074. PMCID: PMC6174196. https://doi.org/10.21037/atm.2018.07.32.

6. Church D, Cardoso L, Kay RG, et al. Assessment and management of anti-insulin autoantibodies in varying presentations of insulin autoimmune syndrome. J Clin Endocrinol Metab. 2018;103(10):3845-55. PMID: 30085133. PMCID: PMC6179165. https://doi.org/10.1210/jc.2018-00972.
7. Zhu Q, Zhao H, Qiu W, et al. Case report: Recurrent autoimmune hypoglycemia induced by non-hypoglycemic medications. Front Immunol. 2022;13:855350. PMID: 35935967. PMCID: PMC9352986. https://doi.org/10.3389/fimmu.2022.855350.
8. Praveen VP, Bhavani N, Jayakumar RV, et al. Autoantibodies to insulin and dysglycemia in people with and without diabetes: An underdiagnosed association. Clin Diabetes. 2016;34(3):164-7. PMID: 27621535. PMCID: PMC5019007. https://doi.org/10.2337/diaclin.34.3.164.
9. Tadakamalla Y, NS Praveen, Sethi BK, Gowde CDK. Treatment of insulin autoimmune syndrome - a tri-prong approach. J Diabetes Treat. 2021;6:1094. https://doi.org/10.29011/2574-7568.001094.
10. Wong SL, Priestman A, Holmes DT. Recurrent Hypoglycemia from Insulin Autoimmune Syndrome. J Gen Intern Med. 2014;29(1):z250-4. PMID: 23979685. PMCID: PMC3889959. https://doi.org/10.1007/s11606-013-2588-9.
11. Peters C, Nirmalaraj K. Long-Term Prevention of Hypoglycemia by Conservatively Managed Insulin Autoimmune Syndrome. AACE Clinical Case Rep. 2016;2(3):e260-3. https://doi.org/10.4158/EP15991.CR.