CASE REPORT

Spontaneous hypoglycaemia in a patient with Graves' disease

Buddhi Paudyal,¹ Mila Shakya,² Buddha Basnyat²¹Department of Internal Medicine, Patan Academy of Health Sciences, Kathmandu, Nepal²Oxford University Clinical Research Unit, Patan Hospital, Kathmandu, Nepal**Correspondence to** Professor Buddha Basnyat, buddhabasnyat@gmail.com

Accepted 8 March 2016

SUMMARY

A 23-year-old man, on treatment for Graves' disease, presented to the emergency department, with 2 separate episodes of loss of consciousness. During the first episode, the initial serum glucose was 19 mg/mL, and 44 mg/dL during the second episode. The patient was non-diabetic, and had elevated blood insulin, C peptide and insulin antibody levels. His abdominal radiographic findings were normal. He was diagnosed with Hirata disease, and put on propylthiouracil as a replacement for carbimazole. Hypoglycaemia was managed with dextrose infusions and frequent meals. The patient's condition improved and he had no further episodes of hypoglycaemia during the follow-up period.

BACKGROUND

Insulin autoimmune syndrome (IAS, Hirata disease) is characterised by a combination of fasting or postprandial hypoglycaemia, high serum insulin levels and presence of insulin autoantibodies in the absence of exogenous insulin administration.¹ Hypoglycaemia, in the absence of a glycaemic-lowering agent, can present as a diagnostic challenge. Failure to recognise the underlying cause of spontaneous hypoglycaemia can have potentially fatal consequences. We report a case of IAS in South Asia—where the condition has been virtually unreported—induced by a commonly used antithyroid drug.

CASE PRESENTATION

A 23-year-old Nepali man was brought to the emergency department (ER) in an unconscious state. He had no history of fever, headache, vomiting, weight loss or seizure-like activity. His Glasgow Coma Scale (GCS) score was 6 (E2V1M3) at the time of presentation. He was of normal weight (body mass index 23.13 kg/m²) and his vitals were stable (blood pressure 130/70 mm Hg, pulse rate 72/min). Physical examination revealed a diffusely enlarged, non-tender thyroid. The rest of the examination revealed no abnormalities. Two years ago, the patient had been diagnosed as having Graves' disease, and was on carbimazole 30 mg/day. After a lapse in medication for around 3 months, the patient had restarted his treatment 6 weeks back. He had no history of diabetes mellitus, no other concurrent illnesses and no exposure to insulin or antidiabetic agents. He was on a normal diet. There was no family history of diabetes mellitus. On investigation, his random blood glucose was 19 mg/dL. All other routine laboratory tests were within normal limits. The patient regained

consciousness after hypoglycaemia was corrected with intravenous dextrose infusion. He was sent home and advised to follow-up for evaluation in the medical outpatient department. Four days later, the patient was found unconscious on his bed and brought to the ER again. History and examination did not reveal any findings at variance with those of the previous episode. The patient had persistent hypoglycaemia despite intravenous dextrose infusion, and was admitted to the hospital for further evaluation.

INVESTIGATIONS

During the second ER visit, the patient's initial random blood glucose was 44 mg/dL. Repeat random blood glucose after dextrose infusion was 10 mg/dL. During the hospital stay, six hourly random blood glucose revealed recurrent episodes of hypoglycaemia (ranging from 37 to 49 mg/dL), usually in the early mornings. Blood test revealed haematocrit of 40% and leucocyte count of $6.3 \times 10^3/\mu\text{L}$ with 86% neutrophils, 12% lymphocytes and 2% eosinophils. Liver and kidney function tests (including serum sodium and potassium levels) were within normal limits. FT3 and FT4 were elevated (22.4 pg/mL and 5.88 ng/mL, respectively; normal: 2.77–5.27 and 0.78–2.19, respectively), and thyroid-stimulating hormone level was low (0.015 $\mu\text{IU/mL}$; normal: 0.46–4.68). Antithyroid peroxidase level was >1300 IU/mL (positive >60). Ultrasound of the thyroid revealed an enlarged thyroid with hypoechoic echotexture. CT scan and MRI of the abdomen were normal. There was no evidence of pancreatic or extrapancreatic masses. During one of the hypoglycaemic episodes, the serum insulin level was 58.1 $\mu\text{IU/mL}$ (normal: 2–25), C peptide level was 20.7 ng/mL (normal: 0.5–3.2) and insulin antibody level was 88.2 U/mL (positive >18).

DIFFERENTIAL DIAGNOSIS

- Inappropriate use of antidiabetic agents
- Insulinoma
- Insulin-secreting extrapancreatic tumours
- Adrenal insufficiency
- Hirata disease

TREATMENT

The patient was put on 10% dextrose infusion, and all hypoglycaemic episodes were corrected with stat doses of 50% dextrose solution. Carbimazole was changed to propylthiouracil 200 mg thrice daily. Propranolol was stopped as it can mask the symptoms of hypoglycaemia. The patient was

CrossMark

To cite: Paudyal B, Shakya M, Basnyat B. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214801

encouraged to have frequent oral feedings particularly in the early mornings, to avoid hypoglycaemia.

OUTCOME AND FOLLOW-UP

The patient's serum glucose level remained within normal limits after 9 days of hospital admission. The patient was closely monitored for an additional 9 days before he was finally discharged. He was on routine follow-up on an outpatient basis for a year after discharge. He was regularly taking propylthiouracil for Graves' disease, had good control of the disease and had no further episodes of hypoglycaemia.

DISCUSSION

IAS is relatively common among the Japanese population, but rare among other Asians and extremely rare among Caucasians.^{2,3} Since being first reported in Japan, in 1970, by Hirata *et al*,⁴ until 2010, only 21 cases of IAS had been reported in Asia, outside of Japan; these were mostly limited to China and Korea. Among them, 81% had received metformin or carbimazole prior to the development of IAS.² In our part of the world, where thyroid disorders are very common and antithyroid drugs routinely administered, IAS has been virtually unreported. Recently, carbimazole-induced IAS has been reported in a man of Indian descent.⁵ To the best of our knowledge, ours is the first reported case of IAS in Nepal.

Our patient, a known case of Graves' disease, developed IAS at the second treatment with carbimazole, after a brief interruption in between. There have been other reports of patients developing IAS after restarting treatment for Graves' disease.² Insulin antibodies peak 2–3 months after start of antithyroid treatment and the onset of hypoglycaemia in our patient may have been associated with this peak.⁶ Drugs, such as carbimazole, with the sulfhydryl group in their chemical structure, can induce the formation of insulin autoantibodies in predisposed individuals. Although the mechanism is not well understood, the buffering effect of autoantibodies on endogenous insulin released in response to a meal and the subsequent disassociation of insulin from the antibody following decreasing levels of free serum insulin is hypothesised to lead to hypoglycaemia.^{7,8} IAS has also been associated with non-sulfhydryl drugs such as α -lipoic acid,⁹ hydralazine⁸ and imipenem.¹⁰

Hypoglycaemia is uncommon in non-diabetics due to the body's endogenous glucose regulatory mechanism. The most common cause is accidental or iatrogenic administration of glycaemic-lowering agents.¹¹ Our patient presented with neuroglycopenic symptoms, but had no history of diabetes, consumption of any drugs or concurrent critical illness. Abdominal radiography did not reveal any pancreatic or extrapancreatic masses that could have led to excess endogenous secretion of insulin. It would have been ideal to conduct further tests to rule out malignancy with paraneoplastic insulin-like growth factor 2 production; however, in a resource-poor setup such as ours, though useful, the tests would be very expensive and difficult to obtain. Similarly, although adrenal insufficiency can lead to hypoglycaemia, the patient did not reveal any other signs or symptoms suggestive of the disease. Serum sodium and potassium levels in the initial laboratory tests were also normal, due to which the treating physician had a low index of suspicion of the condition. The patient's history of medication for Graves' disease coupled with high insulin level, high anti-insulin antibody level and pattern of postabsorptive hypoglycaemia led to the diagnosis of IAS. Even by the process of exclusion based on the history, physical examination and laboratory findings, Hirata

syndrome was for us the most likely diagnosis here; IAS has additionally been associated with HLA-DR4 alleles.² However, HLA typing is unavailable and costly in our context. It was non-essential for management of the patient, due to which the test was not performed.

Failure to correctly diagnose the cause of recurrent hypoglycaemia in a timely manner can lead to a great burden for the patient. Recurrent spontaneous hypoglycaemia has been associated with high mortality in non-diabetics.² Although IAS was initially associated with East Asians, there have been an increasing number of cases reported outside this group.^{3,12–14}

Clinicians in this part of the world should be aware of IAS as a possible cause of hypoglycaemia, especially in patients with autoimmune disease, such as Graves' disease, who are taking sulfhydryl group medications, which are very commonly used here. A full hypoglycaemic evaluation should include tests for insulin and C peptide, and screening for anti-insulin antibodies.

Learning points

- ▶ Insulin autoimmune syndrome (IAS) should be considered in the differential diagnosis of hypoglycaemia in non-diabetic patients.
- ▶ Introduction of sulfhydryl group compounds can lead to severe recurrent episodes of hypoglycaemia.
- ▶ Hypoglycaemic attacks subside after discontinuation of the offending drug and most cases of IAS have complete remission.
- ▶ Use of medications (immune suppressants, plasmapheresis and corticosteroids) to decrease antibody level is not always necessary.
- ▶ Inability to recognise the condition can lead to fatal consequences.

Contributors BP managed the case. BP, MS and BB contributed to designing and writing the manuscript. BP, MS and BB approved the version to be published.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Hirata Y, Uchigata Y. Insulin autoimmune syndrome in Japan. *Diabetes Res Clin Pr* 1994;24:S153–7.
- 2 Uchigata Y, Hirata Y, Iwamoto Y. Insulin autoimmune syndrome (Hirata disease): epidemiology in Asia, including Japan. *Diabetol Int* 2010;1:21–5.
- 3 Balestrieri A, Magnani E, Ragazzini C, *et al*. Primary insulin autoimmune syndrome in an Italian woman: a case report. *Ital J Med* 2015;9:169–72.
- 4 Hirata Y, Ishizu H, Ouchi N, *et al*. Insulin autoimmunity in a case of spontaneous hypoglycemia. *J Jpn Diabetes Soc* 1970;13:312–20.
- 5 Patwari P, Narasimhan A, Srinivasan R. A case of severe hypoglycemia in a patient with hyperthyroidism. *Endocr Abstr* 2013;32:P996.
- 6 Uchigata Y, Kuwata S, Tokunaga K, *et al*. Strong association of insulin autoimmune syndrome with HLA-DR4. *Lancet* 1992;339:393–4.
- 7 Ichihara K, Shima K, Saito Y, *et al*. Mechanism of hypoglycemia observed in a patient with insulin autoimmune syndrome. *Diabetes* 1977;26:500–6.
- 8 Burch HB, Clement S, Sokol MS, *et al*. Reactive hypoglycemic coma due to insulin autoimmune syndrome: case report and literature review. *Am J Med* 1992;92:681–5.
- 9 Uchigata Y, Hirata Y, Iwamoto Y. Drug-induced insulin autoimmune syndrome. *Diabetes Res Clin Pract* 2009;83:e19–20.

- 10 Lidar M, Rachmani R, Hlaf E, *et al.* Insulin autoimmune syndrome after therapy with imipenem. *Diabetes Care* 1999;22:524–5.
- 11 Martens P, Tits J. Approach to the patient with spontaneous hypoglycemia. *Eur J Intern Med* 2014;25:415–21.
- 12 Chockalingam G, Wilson D, Clifton-Bligh R. Insulin autoimmune syndrome, IAS (Hirata disease) case report. *Endocr Abstr* 2013;32:P289.
- 13 Gomez Cruz MJ, Jabbar M, Saini N, *et al.* Severe hypoglycaemia secondary to methimazole-induced insulin autoimmune syndrome in a 16 year old African-American male. *Pediatr Diabetes* 2012;13:652–5.
- 14 Virally ML, Timsit J, Chanson P, *et al.* Insulin autoimmune syndrome: a rare cause of hypoglycaemia not to be overlooked. *Diabetes Metab* 1999;25:429–31.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow