

Insulin Autoimmune Syndrome – A Case Series

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Insulin autoimmune syndrome, or Hirata's disease, is a rare cause of hypoglycaemia. It is characterised by spontaneous episodes of hypoglycaemia, without any exposure to exogenous insulin. The majority of cases are seen in the Japanese population and it is rarely found to affect other ethnicities. The recognition of this disease is important to avoid unnecessary investigations and procedures. Here, we report two cases of insulin autoimmune syndrome, which were diagnosed and managed in our institute.

Keywords

Insulin autoimmune syndrome, Hirata's disease, post-absorptive hypoglycaemia, insulin autoantibodies, insulin to C-peptide ratio

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Insulin autoimmune syndrome (IAS) is a leading cause of hypoglycaemia in the Japanese population.¹ In India, which has a population of more than 1 billion, only 28 cases of IAS have been reported to date, to the best of our knowledge.^{2–10} IAS is characterised by hyperinsulinaemic hypoglycaemia – elevated insulin autoantibody titres with no prior exposure to exogenous insulin. Most cases of IAS are self-limiting. Here, we report our experience with two cases of this rare disease.

Case 1

A 48-year-old Indian man presented to our endocrine clinic with repeated episodes of severe hypoglycaemia for the past 4 months. These episodes occurred 3–4 hours after meals and were characterised by symptoms of increased hunger, dizziness, palpitations, tremors and diaphoresis. The symptoms were reversed by the patient eating a carbohydrate-based meal. The patient obtained a glucometer and his blood glucose readings during symptomatic episodes varied between 30 and 40 mg/dL. There was no history of fasting hypoglycaemia.

The patient was non-diabetic and had no history of exposure to insulin, insulin secretagogues or any drug known to precipitate hypoglycaemia. He was subjected to an extended oral glucose tolerance test, the results of which are summarised in *Table 1*. The test result revealed a plasma glucose of 33 mg/dL, with corresponding serum insulin of 5,609 µU/mL (normal range -9.2–138.9 µU/mL) and serum C-peptide of 30.9 ng/mL (normal range 1.1–4.4 ng/mL), measured by electrochemiluminescence assay (Roche Diagnostics, Rotkreuz, Switzerland). The molar ratio of insulin to C-peptide was 3:8 (more than 1). The laboratory values raised a suspicion of IAS. To confirm the diagnosis, insulin antibody titres were measured by enzyme immunoassay; the level was more than 300 U/mL (normal range <12 U/mL). The analysis of other autoantibodies (antinuclear antibody, anti-double stranded DNA antibody, anti-neutrophilic cytoplasmic antibody, rheumatoid factor and anti-thyroid peroxidase) was negative.

Other laboratory tests were within normal limits. These included: complete blood count, liver function tests, kidney function tests, thyroid profile, serum cortisol, hepatitis B surface antigen, anti-hepatitis C antibody and HIV antibody tests. Computed tomography (CT) of the patient's abdomen was normal with no abnormality of the pancreas. A gallium-68 DOTANOC scan of the whole body did not reveal any suspicious lesions.

The patient was initiated on frequent low-carbohydrate meals. Subsequently, he had spontaneous resolution of hypoglycaemia after 6 months of initial presentation. At the end of 6 months, his insulin autoantibody titres were 1.2 U/mL.

Case 2

A 50-year-old Indian man presented to our clinic with recurrent hypoglycaemia for the past month. These episodes were characterised by neuroglycopenic symptoms with documented glucose values on glucometer varying from 35 to 60 mg/dL. These symptoms were corrected by the intake of a carbohydrate-based diet, thus fulfilling Whipple's triad. These episodes occurred 5–6 hours after meals. There was no history of exposure to insulin, oral hypoglycaemic agent or any drug known to precipitate hypoglycaemia. The patient was non-diabetic.

Table 1: Results of extended oral glucose tolerance test – patient 1

Time (hours)	Plasma glucose (mg/dL)	Serum insulin (μ U/mL) (1:10 dilution)	C-peptide (ng/mL)
0	65	3,411	25.4
1	220	3,996	39.6
2	194	8,889	47.4
3	94	7,295	39.4
4	33	5,609	30.8

The patient was admitted for evaluation of hypoglycaemia. An extended oral glucose tolerance test revealed an end-of-test blood glucose of 50 mg/dL, with a corresponding insulin level of 6,154 μ U/mL and a C-peptide of 19.6 ng/mL, measured by electrochemiluminescence assay (Table 2). Insulin to C-peptide molar ratio was 1.1 (more than 1). The results of both the gallium-68 DOTANOC scan and the exendin scan were within normal limits. To confirm the diagnosis, insulin autoantibody titres were measured, which were 68.8 U/mL.

This patient was also started on frequent, small, low-carbohydrate meals. He has not had any recurrence of hypoglycaemia so far (1 year after diagnosis) and is under follow-up care.

Discussion

IAS – or Hirata's disease – is a rare case of hyperinsulinaemic hypoglycaemia. This condition was first described by Hirata et al. in 1970.¹¹ There is a strong association with HLA-DR4.¹² Unfortunately, due to resource constraints, HLA genotyping could not be done in our patients.

Patients with IAS usually present in adulthood, and there is no predilection for any gender. Hypoglycaemic episodes usually occur in the post-absorptive state, although there have also been reports of fasting-and-exercise-induced hypoglycaemia.¹³ IAS is commonly associated with other autoimmune conditions, such as Graves' disease, systemic lupus erythematosus, rheumatoid arthritis and ankylosing spondylitis. Neither of our patients had a history of any other associated autoimmune condition.

Most patients also have exposure to drugs prior to the precipitation of hypoglycaemia. Common drugs that are implicated are methimazole, carbimazole, glutathione, tiopronin, interferon- α , captopril, diltiazem, hydralazine, procainamide, isoniazid, D-penicillamine, imipenem and penicillin G.¹⁴ Alpha-lipoic acid – a popular health supplement – has also been linked to IAS.¹⁵ In another case report from our institute, proton pump inhibitors were found to induce hypoglycaemia.²

The mechanism of hypoglycaemia in IAS is assumed to be caused by the presence of large amounts of insulin autoantibodies (IAA). After food, there is a rise in blood glucose, followed by an increase in insulin levels. Insulin is then bound by IAA, making the insulin ineffective, which then leads to postprandial hyperglycaemia. This triggers the production of increased amounts of insulin and C-peptide to cope with the postprandial hyperglycaemia. Insulin-IAA complexes create a reserve of insulin: when dissociation occurs, there is a sustained release of free insulin in the post-absorptive state, leading to more prolonged and severe hypoglycaemia. Sulfhydryl group drugs act as haptens; they interact with the disulphide bonds of insulin and augment its immunogenicity.

Table 2: Results of extended oral glucose tolerance test – patient 2

Time (hours)	Plasma glucose (mg/dL)	Serum insulin (μ U/mL) (1:10 dilution)	C-peptide (ng/mL)
0	76	4,438	18.8
1	212	7,043	30.2
2	200	10,412	40.0
3	103	9,060	28.3
4	51	7,900	22.2
5	50	6,154	19.6

Common differential diagnoses of IAS include insulinoma and exogenous intake of insulin and sulphonylureas. The differences between insulinomas and IAS are summarised in Table 3. Another differential diagnosis of IAS is hypoglycaemia caused by late dumping syndrome. The salient points between IAS and late dumping syndrome are covered in Table 4.

The measurement of insulin autoantibody titres is mandatory for the diagnosis of IAS.¹⁶ However, a common shortcoming in most of the commercially available assays is that only the immunoglobulin-G class of insulin autoantibodies may be detected.¹ Hence, results may be falsely negative if autoantibodies are of a different class.¹ In that case, precipitation of serum with polyethylene glycol (PEG), followed by recovery of insulin in the supernatant, may serve as an indirect measure for detecting insulin autoantibodies.¹⁷ In cases of suspected IAS, there is a marked difference in the levels of serum total and free insulin after PEG precipitation.³ In IAS, after PEG precipitation, levels of bound insulin are usually much higher, while those of free insulin are lower; the reverse is seen in healthy controls.³

The molar ratio of insulin to C-peptide may be used as a marker for the diagnosis of IAS. Insulin and C-peptide are secreted from the beta cells in equimolar concentrations, but insulin is cleared rapidly, with a half-life of 5 minutes, whereas C-peptide has a half-life of 30 minutes. Therefore, in normal individuals and insulinomas, the insulin to C-peptide molar ratio is less than 1.¹⁸ This ratio is greater than 1 in two conditions; namely, IAS and exogenous insulin administration, where C-peptide is suppressed.¹⁸ In both our patients, the insulin to C-peptide molar ratio was greater than 1.

There are usually no pathological abnormalities of the pancreas in IAS, but hyperplasia of pancreatic islets has been reported in one patient.¹⁹ In another case of IAS, nesidioblastosis was reported on pancreatic biopsy.²⁰

Most cases of IAS are self-limiting, with resolution of symptoms taking place within 3–6 months of initial diagnosis.¹ The exact mechanism of self-resolution is not known, yet circumstantial evidence suggests that when the antigen (e.g. the sulfhydryl drug) is withdrawn, the antibodies may wear off over a period of time.¹ Cappellani et al. have demonstrated that in IAS induced by alpha-lipoic acid, the insulin auto-antibody levels fell off after the inciting agent (i.e. alpha-lipoic acid) was withdrawn.²¹

In patients with intractable hypoglycaemia, the first-line treatment includes small, frequent meals that are low in carbohydrate,

Table 3: Differences between insulin autoimmune syndrome and insulinoma

Parameter	Insulin autoimmune syndrome	Insulinoma
Timing of hypoglycaemia	Post-prandial	Fasting
Associated conditions	Other autoimmune conditions, such as Graves' disease, rheumatoid arthritis, SLE Also, MGUS, multiple myeloma	Multiple endocrine neoplasia 1
Prior exposure to drugs	Yes (drugs that are commonly implicated are methimazole, carbimazole, glutathione, alpha lipoic acid, proton pump inhibitors)	No
Serum insulin levels	Markedly elevated (usually more than 1,000 µU/ml)	Moderately elevated (less than 1,000 µU/ml)
Insulin to C-peptide ratio	More than 1	Less than 1
Abdominal imaging	Normal	Focal lesion in the pancreas, showing positive uptake on exendin scan or gallium-68 DOTANOC
Treatment	Self-limiting course; in intractable cases, treatment options are frequent low-carbohydrate meals, steroids, steroid-sparing immuno-suppressants	Excision of the lesion

MGUS = monoclonal gammopathy of undetermined significance; SLE = systemic lupus erythematosus.

Table 4: Salient points between insulin autoimmune syndrome and late dumping syndrome

Features	IAS	Late dumping syndrome
Preceding history of gastric bypass surgery	Absent	Present
Timing of hypoglycaemia	1–3 hours after meals	1–3 hours after meals
Type of hypoglycaemia	Hyperinsulinaemic hypoglycaemia	Hyperinsulinaemic hypoglycaemia
History of offending drug	Present	Absent
High-carbohydrate diet consumption preceding hypoglycaemia	Present	Present
Gastrointestinal vasomotor symptoms (shock, syncope, near syncope)	Absent	Present
Insulin autoantibodies	Present	Absent
Self-resolution	Present	Absent
Primary therapy	Dietary management, acarbose, corticosteroids, rituximab, azathioprine, cyclophosphamide, plasmapheresis	Dietary management, acarbose, octreotide
Surgery	Pancreatectomy in intractable cases	Stomal revision, Billroth II to Billroth I anastomoses, pyloric reconstruction, jejunal interposition, and Roux-en-Y conversion

IAS = insulin autoimmune syndrome.

to avoid postprandial hyperglycaemia and a subsequent rise in insulin. Short courses of corticosteroids (oral prednisolone 30–60 mg) may be used as adjunct therapy.^{22,23} Other agents of treatment include acarbose (to reduce carbohydrate absorption), diazoxide, octreotide and partial pancreatectomy (to restrict insulin release) and plasmapheresis (to reduce insulin autoantibody titres).^{20,22,24,25} Immunosuppressants, such as azathioprine, cyclophosphamide and mycophenolate mofetil also have been tried in IAS.^{4,26,27} Rituximab, an anti-CD20 monoclonal antibody, has also been used successfully in a few intractable cases where there was a failure of response to steroids.^{28–31}

Conclusion

We have described two cases of IAS, a rare cause of endogenous hyperinsulinaemic hypoglycaemia. IAS should be suspected in any patient usually presenting with postprandial hypoglycaemia, with an unusually high insulin concentration, and moderately raised pro-insulin and C-peptide levels. The insulin to C-peptide molar ratio is more than 1 in IAS. The diagnosis can be confirmed by the measurement of insulin autoantibody titres. An appropriate diagnosis may avoid unwarranted investigations and abdominal exploration. Most cases are self-limiting, while a few intractable cases may require dietary modifications, corticosteroids or steroid-sparing immunosuppressants. □

- Censi S, Mian C, Betterle C. Insulin autoimmune syndrome: from diagnosis to clinical management. *Ann Transl Med.* 2018;6:335.
- Gopal K, Priya G, Gupta N, et al. A case of autoimmune hypoglycaemia outside Japan: Rare, but in the era of expanding drug-list, important to suspect. *Indian J Endocrinol Metab.* 2013;17:1117–9.
- Raizada N, Rahaman SH, Kandasamy D, Jyotsna VP. Rare association of insulin autoimmune syndrome with ankylosing spondylitis. *Endocrinol Diabetes Metab Case Rep.* 2015;2015:150090.
- Panikar V, Joshi S, Vadgama J, et al. Autoimmune hypoglycemia relapse on glucocorticoids, effectively treated with azathioprine. *J Assoc Physicians India.* 2018;66:78–9.
- Gite J, Shrivastav R, Bhasin N, et al. Recurrent hypoglycaemia due to insulin autoimmune disease (Hirata disease) associated with monoclonal gammopathy of unknown significance. *J Assoc Physicians India.* 2015;63:68–9.
- Munigoti S, Harinarayan C. A rare case of autoimmune hypoglycaemia. *J Clin Sci Res.* 2017;6:245–8.
- Alam S, Ozair M, Ahmad J. Hypoglycemia due to insulin autoimmune syndrome: A rare cause not to be forgotten. *J Clin Transl Endocrinol Case Rep.* 2016;2:7–9.
- Manjunath P, George B, Mathew V, et al. "Riding high on low fuel" - Our experience with endogenous hyperinsulinemic hypoglycemia. *Indian J Endocrinol Metab.* 2017;21:655–9.
- Patel M, Shah R, Ramteke-Jadhav S, et al. Management of insulin autoimmune hypoglycaemia: Single-centre experience from Western India with systematic review of world literature. *Clin Endocrinol (Oxf).* 2020;92:409–20.
- Manjunath P, Pavithran P, Bhavani N, et al. Insulin autoantibody syndrome: Varying clinical presentations and response patterns of an underrecognized entity. *Indian J Endocrinol Metab.* 2019;23:540–4.
- Hirata Y, Ishizu H, Ouchi N, et al. Insulin autoimmunity in a case of spontaneous hypoglycaemia. *J Jpn Diabetes Soc.* 1970;13:312–20.
- Uchigata Y, Kuwata S, Tokunaga K, et al. Strong association of insulin autoimmune syndrome with HLA-DR4. *Lancet.* 1992;339:393–4.

13. Wong SL, Priestman A, Holmes DT. Recurrent hypoglycemia from insulin autoimmune syndrome. *J Gen Intern Med.* 2014;29:250–4.
14. Uchigata Y, Hirata Y, Iwamoto Y. Drug-induced insulin autoimmune syndrome. *Diabetes Res Clin Pract.* 2009;83:e19–20.
15. Ishida Y, Ohara T, Okuno Y, et al. α -lipoic acid and insulin autoimmune syndrome. *Diabetes Care.* 2007;30:2240–1.
16. Ismail AAA. Testing for insulin antibodies is mandatory in the differential diagnosis of hypoglycaemia in nondiabetic subjects: Letters to the Editor. *Clin Endocrinol (Oxf).* 2012;76:603–4.
17. Arnlqvist H, Olsson PO, von Schenck H. Free and total insulin as determined after precipitation with polyethylene glycol: analytical characteristics and effects of sample handling and storage. *Clin Chem.* 1987;33:93–6.
18. Lebowitz MR, Blumenthal SA. The molar ratio of insulin to C-peptide. An aid to the diagnosis of hypoglycemia due to surreptitious (or inadvertent) insulin administration. *Arch Intern Med.* 1993;153:650–5.
19. Uchigata Y, Hirata Y. Insulin autoimmune syndrome (IAS, Hirata disease). *Ann Med Interne (Paris).* 1999;150:245–53.
20. Woo C-Y, Jeong JY, Jang JE, et al. Clinical features and causes of endogenous hyperinsulinemic hypoglycemia in Korea. *Diabetes Metab J.* 2015;39:126.
21. Cappellani D, Sardella C, Campopiano MC, et al. Spontaneously remitting insulin autoimmune syndrome in a patient taking alpha-lipoic acid. *Endocrinol Diabetes Metab Case Rep.* 2018;2018:18–1022.
22. Schlemper R, Uchigata Y, Frolich M, et al. Recurrent hypoglycaemia caused by the insulin autoimmune syndrome: the first Dutch case. *Neth J Med.* 1996;48:188–92.
23. Chu J-P, Zheng X-W, Lu J, et al. Insulin-induced autoimmune syndrome: A case report. *Exp Ther Med.* 2016;12:3359–62.
24. Philippon M, Sèjil S, Mugnier M, et al. Use of the continuous glucose monitoring system to treat insulin autoimmune syndrome: quantification of glucose excursions and evaluation of treatment efficacy. *Diabet Med.* 2014;31:e20–4.
25. Peters C, Nirmalaraj K. Long-term prevention of hypoglycemia by conservatively managed insulin autoimmune syndrome. *AACE Clin Case Rep.* 2016;2:e260–3.
26. Rouabhia S, Ramanoelina J, Godmer P, et al. Insulin autoimmune syndrome revealing systemic lupus erythematosus. *Ann Med Interne (Paris).* 2003;154:59–60.
27. Greenfield JR, Tuthill A, Soos MA, et al. Severe insulin resistance due to anti-insulin antibodies: response to plasma exchange and immunosuppressive therapy. *Diabet Med.* 2009;26:79–82.
28. Saxon DR, McDermott MT, Michels AW. Novel management of insulin autoimmune syndrome with rituximab and continuous glucose monitoring. *J Clin Endocrinol Metab.* 2016;101:1931–4.
29. Church D, Hunter RW, Lyall M, et al. Resolution of hypoglycemia and cardiovascular dysfunction after rituximab treatment of insulin autoimmune syndrome. *Diabetes Care.* 2017;40:e80–2.
30. Kroemer TM, Erler A, Tsourdi E, et al. Immunoadsorption followed by rituximab as a definitive treatment for insulin autoimmune syndrome (Hirata syndrome): A case report. *Diabetes Care.* 2018;41:e23–4.
31. Chen AX, Belligaswate A, White G, Burt MG. Rituximab for treatment of refractory insulin autoimmune syndrome associated with non-Hodgkin B-cell lymphoma. *Clin Endocrinol (Oxf).* 2019;91:230–2.