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

Disclosures: Hiya Boro, Uttio Gupta, Charandeep Singh, Rakhi Malhotra and Rajesh Khadgawat have no financial or non-financial relationships or activities to declare in relation to this article.


Compliance with Ethics: Informed consent was received from the patients involved in this case report and no identifying information or images have been included.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Access: This article is freely accessible at touchENDOCRINOLOGY.com © Touch Medical Media 2020.

Received: 22 May 2020
Accepted: 27 July 2020
Published Online: 30 September 2020
Citation: European Endocrinology. 2020;16(2):168–71
Corresponding Author: Hiya Boro, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India. E: hiya21288@gmail.com

Support: No funding was received in the publication of this article.

Insulin autoimmune syndrome (IAS) is a leading cause of hypoglycaemia in the Japanese population. 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. 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 <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.
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 µU/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. There is a strong association with HLA-DR4. 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. 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. Alpha-lipoic acid – a popular health supplement – has also been linked to IAS. There are usually no pathological abnormalities of the pancreas in IAS, but hyperplasia of pancreatic islets has been reported in one patient.

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. Sulphhydryl group drugs act as haptons; they interact with the disulphide bonds of insulin and augment its immunogenicity.

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. However, a common shortcoming in most of the commercially available assays is that only the immunoglobulin-G class of insulin autoantibodies may be detected. Hence, results may be falsely negative if autoantibodies are of a different class. 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.

In cases of suspected IAS, there is a marked difference in the levels of serum total and free insulin after PEG precipitation. 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.

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. This ratio is greater than 1 in two conditions; namely, IAS and exogenous insulin administration, where C-peptide is suppressed. 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. In another case of IAS, nesidioblastosis was reported on pancreatic biopsy.

Most cases of IAS are self-limiting, with resolution of symptoms taking place within 3–6 months of initial diagnosis. The exact mechanism of self-resolution is not known, yet circumstantial evidence suggests that when the antigen (e.g. the sulphhydryl drug) is withdrawn, the antibodies may wear off over a period of time. 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.

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

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

IAS = insulin autoimmune syndrome; MGUS = monoclonal gammopathy of undetermined significance; SLE = systemic lupus erythematosus.

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

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

IAS = insulin autoimmune syndrome.

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.

References