Insulin Autoimmune Syndrome, IAS (Hirata disease) Case report


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Introduction

- Insulin Autoimmune Syndrome was first described in 1973 by Hirata, characterised by recurrent spontaneous postprandial hypoglycaemia.
- Serum insulin concentrations are extremely high associated with elevated insulin auto antibodies.
- There have been more than 170 cases reported worldwide. We report the first case of IAS in Australia.
- The incidence of IAS in Caucasians is one-tenth of that in Japanese populations. The peak age at onset is 60-69 years with no gender difference. Approximately 82% of IAS patients have a spontaneous remission.
- Insulinomas are the most prevalent cause of hyperinsulinenic hypoglycaemia in Caucasians.
- Primary investigation is always focused on their localization followed by surgery.

Case Report

- A 81 year old female (of Argentinean heritage) presented with a three month history of progressively worsening symptoms of intermittent, late postprandial diaphoresis, tremors, palpitations, dizziness and confusion.
- Symptoms improved with the administration of sugary drinks and other caloric intake resulting in a weight gain of 3 kg over 2 months.
- At presentation blood glucose level (BGL) was 1.2mmol/L.
- She required continuous 50% dextrose to maintain BGL above 6-7mmol/L.
- When her plasma glucose measured 1.9mmol/L, serum insulin was elevated > 2400 mU/L (<27), C-peptide 11.7mmol/L (0.4-1.5).
- Sulphonylurea screening was negative.

Abdominal CT, MRI and a Gallium-Dotatate PET scan all failed to confidently identify an insulinoma.

Management

- An endoscopic ultrasound found an 8 mm lesion thought to be a lymph node adjacent to the pancreas.
- Selective arterial calcium stimulation and hepatic venous sampling demonstrated high insulin concentrations across the pancreas without a gradient (Table 1).
- On the basis of the endoscopic ultrasound findings, laproscopy with intraoperative ultrasound failed to identify an insulinoma; biopsy of the pancreatic tail showed normal islet cells.
- She developed a fistula post-operatively with a chylous ascitic leak requiring rectal sheath suture.
- The diagnosis of Hirata disease was made on demonstration of elevated insulin auto antibodies at >50U/L (<0.3).
- She was treated with Prednisone starting at 50mg which was tapered over 12 weeks to a maintenance dose of 5mg.
- She was weaned off steroids after 5 months. No hypoglycaemic episodes since then. Fasting glucose 4.0, Insulin 13, Proinsulin 13.3pmol/L, C-peptide 1.1 (all normal). Insulin antibodies 12.47 U/ml (<0.3) and falling.

Discussion

- The postulated mechanism behind Insulin Autoimmune Syndrome (Hirata Disease) is that antibodies directed against insulin disrupt the normal relationship between glucose and insulin.
- The buffering effect of antibodies results in binding and release of secreted insulin out of synchrony with the prevailing glucose concentration leading to severe postprandial hypoglycaemia.
- Free insulin levels are normal though bound (total) levels are high. Altered insulin kinetics post glucose tolerance testing is often observed sometimes with a diabetic glycaemic pattern.
- Although not evident in our patient, development of IAS in some individuals has been associated with exposure to sulphydryl compounds. These compounds are thought to interact with disulphide bonds rendering insulin more immunogenic.
- IAS is strongly associated with HLA class II alleles: DRB1*0405/ DQA1*0301/ DQB1*0302.
- The insulin antibodies of IAS patients are reportedly of the IgG class with wide distribution from IgG1 to IgG4.
- Our case highlights an important differential diagnosis and the need to measure insulin antibodies in such cases, to avoid potentially unnecessary surgery.
- Patients are best treated with conservative support and possibly immunosuppressive therapy.

References


Table 1. Hepatic venous insulin levels (mU/L) following selective arterial calcium stimulation.

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Insulin level in peripheral blood 3851mU/L