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Case Report

# A not so common syndrome in Europe – Hirata disease

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## Abstract

Insulin autoimmune syndrome (IAS) known as Hirata disease, is a rare cause of hyperinsulinemic hypoglycemia, characterised by recurrent spontaneous postprandial hypoglycemia with elevated insulin levels. It is defined by the presence of high titres of insulin auto-antibodies, with no prior exposure to exogenous insulin and no pathological abnormalities of the pancreatic islets. A 73-year-old Caucasian woman presented with one year history of intermittent hypoglycemia episodes, which had gradually worsened in the past two weeks. Biochemical measurements showed remarkably high fasting insulinemia with levels >1000 uUi/ml and post prandial plasma glucose levels (PG) between 40 and 32 mg/dl, glycated hemoglobin concentration was 5.8 % (pre-diabetes) and the abdominal computer tomography (CT) did not show abnormalities. The 72 hours fasting test was negative. Four hours after mixed meal, the patient developed hypoglycemia with glucose levels (PG) of 34 mg/dL. Fasting insulin levels were 495 Ui/l and insulin autoantibodies (IAA) were positive 1900 u/ml (normal range <0.4) leading to the diagnosis of Hirata disease. **Conclusion:** We report a case of spontaneous postprandial hypoglycemic episodes with highly elevated levels of insulin and insulin auto-antibodies (Hirata disease) in a Caucasian patient.

**Keywords:** Hirata disease, hyperinsulinemia, hypoglycemia, autoimmune, IAS.

## Introduction

Insulin autoimmune syndrome (IAS) known as Hirata disease is a rare cause of hyperinsulinemic hypoglycemia, characterized by recurrent spontaneous postprandial fall in blood glucose with elevated insulin levels. It is defined by the presence of high titres of insulin auto-antibodies, with no prior exposure to exogenous insulin and no pathological abnormalities of the pancreatic islets [1]. More commonly seen in adults than in children, without gender predominance and a mean age of diagnosis of 60-years-old.

It mostly appears in the presence of the human leukocyte antigen (HLA)-DR4 and can be triggered by exposure to drugs containing sulfhydryl group, viruses acting like super-antigens or can appear with no apparent cause [2–4]

## Case Report

We admitted a 73-year-old Caucasian woman with one year history of intermittent hypoglycemia episodes, gradually worsened in the past two weeks. Medical history was significant for hypertension, vitiligo, and essential tremortreated with beta-blockers and pramiracetam. The patient had no personal or familial history of diabetes mellitus and no evidence for use of oral antidiabetic medication, exogenous administration of insulin, bariatric surgery, or intensive physical exercise. She denied any history of alcoholism or smoking.

Prior to our admission, the patient was hospitalized in another hospital, where blood tests showed remarkably highfasting insulinemia with levels >1000 uUi/ml (normal range 1.9–23uUi/ml) and postprandial venous PG

showed levels between 40 and 32 mg/dl, glycated hemoglobin concentration was 5.8% (pre-diabetes), complete blood count showed normocytic anemia, mild leucocytosis, and no other abnormalities were noticed. An abdominal computer tomography (CT) scan was performed to determine the cause of spontaneous hypoglycemia. The CT scan showed no abnormalities, thus excluding a potential insulinoma.

On examination, the patient appeared alert and oriented to person and time. She had normal vital signs, with no physical and neurological anomalous findings. Her body mass index (BMI) was 28 kg/m$^2$. Biochemical measurements showed normal fasting glycemia (92 mg/dl) and high fasting insulinemia 495 uUi/ml (normal range 1.9–23uUi/ml).

We performed a 72 hours fasting test, which was negative as the patient did not develop hypoglycemic symptoms, therefore excluding insulinoma and other causes of fasting hypoglycemia. During the test PG ranged from 92–66 mg/dl, with gradually increasing levels of ketone bodies in serum (finger-prick testing for beta-hydroxybutyrate), showing a physiological response to fasting. After the fasting test, four hours after a meal, the patient did develop hypoglycemia. We performed blood tests during the episode and the results showed PG of 34 mg/dL with an abnormal elevated insulin level >1000 Ui/l .

Taking into consideration the postprandial hypoglycemia with extremely elevated levels of serum insulin and also the negative 72 hours fasting test, negative abdominal CT scan and ultrasonography for insulinoma, two possible diagnoses remained :1) pre-type 2 diabetes state with insulin resistance and functional hypoglycemia and 2) autoimmune insulin syndrome also know as Hirata's disease. The insulin autoantibodies (IAA) resulted positive 1900 u/ml (normal range <0.4) and the anti-insulin receptor antibodies (AIRA) were negative. These results directed us towards the diagnosis of Hirata's disease. As it is cited in the literature, Hirata's disease is known to be associated with hematological and autoimmune diseases, especially monoclonal gammopathy of undetermined significance (MGUS) so we investigated for both. Protein electrophoresis and immunoelectrophoresis came back negative for MGUS. It is to be noted that the patient reported being affected by vitiligo, an autoimmune condition of the skin.

For this patient with pre-diabetes and positive IAA we considered additional anti islet cell antibodies test: islet tyrosine phosphatase 2 (IA2) and glutamic acid decarboxylase(GAD) auto antibodies which resulted negative. Also post prandial functional hypoglycemia was never reported, in our knowledge in pre clinical type 1 diabetes.

Hirata's disease responds to the treatment of the underlying pathology and, when idiopathic, tends to be auto limited. In our patient we started a specific diet based on 6 meals per day, with reduction of carbohydrates, especially rapidly absorbable (160 g carbohydrates per day), moderate in fat, and high in protein (70 g/day protein). It was indicated that all meals contain protein and high levels of fibres and to avoid highly concentrated carbohydrates. Another aspect that was taken into consideration as a target for treatment was the insulin resistance due to the metabolic syndrome. Consequently, we decided to prescribe 500 mg of metformin, two-times a day, with up-titration to 1000 mg two-times per day. She received additional treatment with angiotensin-converting enzyme, beta-blockers and statin. The patient was discharged on day 8 of admission.

Given that the patient did not have any other new episodes of hypoglycemia after the beginning of diet and treatment, we considered the prognosis and the evolution of the disease favorable. The patient was re-evaluated at six months and showed some minor intentional weight loss, a glycated hemoglobin of 5.6%, no hypoglycemia episodes, no anemia or other abnormalities of the blood work.

## Discussion

Insulin autoantibody syndrome (IAS), is a rare syndrome, firstly discovered in 1970 by Yukimasa Hirata et al. as a cause of postprandial hyperinsulinemichypoglycemic episodes [5–8]. Since then, approximately 400 cases have been reported.[9]Most of the cases, roughly 90% of them, occurred in the Japanese population. A


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strong connection between IAS and the presence of the human leukocyte antigen (HLA)-DR4 has been discovered, being the third leading cause of spontaneous hypoglycemic episodes, after insulinoma and extra pancreatic neoplasia in Japan [3,4,6]. The age of onset is 60–70 years, without any certain gender predilection [5]. Many of the patients, approximately 80–85% of them, have other autoimmune disease or hematological disorders, such as rheumatoid arthritis, Graves disease, systemic lupus erythematosus, chronic hepatitis or vasculitis, monoclonal gammopathy or multiple myeloma, with the last two described in the Caucasian population [3, 10]. IAA can appear spontaneously or can be triggered by prior exposure to certain drugs containing sulfhydryl groups, frequently by anti-thyroid drugs (ATD) mainly by methimazole [11] but also by propylthiouracil and carbimazole and by dietary supplements containing alpha lipoic acid used in diabetic neuropathy [12], anti-aging supplements, polycystic ovary syndrome. Viruses acting like super-antigens(rubella, coxsackie B, influenza, mumps, hepatitis C) can also be a trigger. [2, 3, 11, 13]. In the case of drug induced IAS, the clinical manifestations of the disease begin following the 4–6 weeks after exposure to certain drugs mentioned above, but there are some cases in literature in which the clinical manifestation started even after years [2].

The main characteristic is hypoglycemia and, depending upon its severity, it can be accompanied by autonomic symptoms (hunger, sweating, tremor, palpitation, paresthesia, anxiety) and neuroglycopenic symptoms (fatigue, seizures, loss of consciousness) [2, 3]. In a healthy individual, symptoms start to appear at glucose levels below 55 mg/dl but in patients suffering from IAS, the limit is lower. Postprandial hypoglycemia is due to the mechanism of the appearance of IAS. The core of IAS is the presence of the circulating insulin autoantibodies, mainly the IgG subtype, but there are also some cases with IgA and IgM, making it harder to diagnose because most of the kits only identify IgG. Polyethylene glycol (PEG) test should be considered as a test that can identify any type of Ig [3, 10, 14]. Insulin autoantibodies (IAA) have a high capacity and low affinity of binding insulin leading to hypoglycemic episodes related with the insulin peaks after a meal, explaining why it is important to understand the timing of the episodes, unlike insulinoma where the 73% of the patients have fasting hypoglycemia [15, 16].

The pathogenic mechanism of hypoglycemia is not yet clearly understood [17]. It is believed that after food intake, the auto-antibody binds immediately to insulin, leading to postprandial hyperglycemia. The insulin is later released by the dissociation of the antibody-insulin complex, causing hypoglycemia [5, 17, 18].

Literature cases of insulin autoantibodies (IAA) related with exogenous administration of insulin in DM type 1, noticing a milder hypoglycemia due to the low capacity and high affinity of binding insulin are worth mentioning, here [2].

The laboratory tests showed remarkably increased insulin levels, much higher than the levels found in insulinoma. C-peptide and proinsulin levels tend to be higher or to remain at normal levels. A criterion for diagnosis can be the insulin to C-peptide ratio, a normal range is lower than 1, even though they are co-secreted by the pancreatic B-cells in equimolar proportion, explained by the half-life of insulin (5–10 min) and half-life of C-peptide (30–35 minute), the latter one has a slow metabolism process through the kidneys compared to the rapid metabolism pathway of the liver. In IAS the ratio is >1 because of the formation of the antibody- insulin complex causing the delay in the metabolization of insulin.[3, 16, 19]. Glycated hemoglobin levels can be variable, from normal to high values, depending on the severity and frequency of the hypoglycemic episodes [2, 3]. *The gold standard* to confirm the diagnosis of IAS is the measurement of the insulin autoantibodies (IAA).

Most of the patients have a spontaneous remission in one to three months after the first episode [1, 20]. The prevention of the hypoglycemic episodes mainly consists of the dietary approach, where the patient is advised to have frequent meals and to avoid the intake of sweets, sugar and to frequently monitor glucose levels. If the dietary regimen is not enough to prevent the hypoglycemic episodes, the second approach is the use of high dose corticosteroids. Also, an immunosuppressive therapy, such as

azathioprine and rituximab, can be taken into consideration in case of persistency of the disease which demonstrated a high rate of success. When the pharmacological therapy is not effective, plasmapheresis can be tried [2].

## Conclusion

We report a case of spontaneous postprandial hypoglycemia episodes with highly elevated levels of insulinemia and insulin autoantibodies, leading us to the rare diagnosis of Hirata disease in a Caucasian patient. In this case, the dietary approach and treatment with metformin proved to be successful.

## Conflict of Interest

The authors declare no conflict of interest.

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