

## Case Report

# Hypoglycemia due to insulin autoimmune syndrome (Hirata's disease): a rare cause of hypoglycaemia

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## ABSTRACT

Although the most common cause of recurrent hypoglycaemia is diabetes mellitus as patient is on antidiabetic medications which can be prevented by modification of antidiabetic doses, nutrition therapy and lifestyle modifications. Some endogenous hyperinsulinemic conditions like insulinoma, functional beta cell disorders and insulin autoimmune syndromes, hormonal deficiencies can cause serious and sometimes life threatening hypoglycaemia. So further laboratory evaluation like plasma/serum glucose levels, c-peptide levels, insulin levels, insulin antibodies and imaging studies are needed to evaluate unexplained hypoglycaemia. Here we report a case of insulin autoimmune syndrome in a 67 year old Indian male who had presented to us with multiple episodes of spontaneous hypoglycaemia. On further workup, the patient was found to have endogenous hyperinsulinemic hypoglycemia. As the patient's abdominal imaging revealed no apparent cause of EHH, on further evaluation he came positive for insulin antibodies. Patient was diagnosed as IAS and he was given frequent small meals and complex carbohydrate diet and he had improved symptomatically. The incidence of IAS is most common in Japan and very few cases have been reported from India, so it should be kept in differential diagnosis of recurrent hypoglycaemia.

**Keywords:** Hypoglycemia, Insulin autoimmune syndrome, Antidiabetic, Hirata's disease

## INTRODUCTION

Hirata's disease also called insulin autoimmune syndrome (IAS), is a rare cause of spontaneous hypoglycaemia with insulin auto antibodies in the individuals who are not on exogenous insulin therapy.<sup>1</sup> Hirata et al Was the first to report this case of insulin autoimmune syndrome in 1970 and so many cases have been reported from Japan. This is considered as the third most common cause of hypoglycaemia in Japan, where more than 300 cases of this syndrome have been reported.<sup>2</sup> IAS has association with other autoimmune diseases like Graves' disease and rheumatoid arthritis and association with HLA DR4 has been demonstrated in 96% of Japanese patients with IAS.<sup>3</sup> Interaction of sulfhydryl group with disulfide bond in the insulin

molecule can be major mechanism of action of hypoglycaemia in IAS.<sup>4</sup> The incidence of this IAS disease in INDIA is very low. First case was reported in 2013.<sup>5-7</sup> This can be the most important syndrome in the differential diagnosis of endogenous hyperinsulinemic hypoglycemia (EHH) so that early recognition can be done and unnecessary investigations can be avoided.

## CASE REPORT

We report a case of 67 year old Indian male was referred to our outpatient clinic for evaluation of frequent hypoglycaemia. He was known case of hypertension for 15 years for which he was taking tablet telmisartan+hydrochlorothiazide (40/12.5) OD and tablet aspirin+atorvasatin (75/20) OD. He was non diabetic

presented with complaints of hypoglycemia and one episode of unconsciousness. There was no history of any prior exposure to insulin or any oral antibiotic medications. His symptoms began 1 week back when he used to develop episode of palpitations, sweating, tremors and anxiety which was relieved on ingestion of food. One week after his symptoms began, he had one episode of unconsciousness for which he was taken to hospital where his random blood sugar was found to be 38mg/dl. He regained his consciousness after administration of intravenous 25% dextrose infusion. He was admitted in male medicine ward for further evaluation. General physical examination revealed an alert and healthy male. His weight was 68 kg, height 155cm, BMI 30.8, blood pressure was 140/80 mmHg and pulse rate was 88 BPM. His renal function test, liver function tests, thyroid profile and hemogram were found to be normal. Tests for anti thyroid antibodies, rheumatoid factor and antinuclear antibodies were found to be negative. Serum sulfonyleurea screen was done and found to be negative. His HbA1c was 5.6%. He developed spontaneous hypoglycemia in post absorptive state and his plasma glucose concentration was found to be 47 mg/dl and corresponding serum insulin was >300 µgm and C peptide was 15.2 ng/ml. Insulin levels were measured by chemiluminescent micro particle immune assay (CMIA) method. For his presenting complaints he was admitted in cardiology ward for CAG, where CAG was done and revealed non critical coronary artery disease. At that time he had 2-3 episodes of hypoglycemia and he was taken to male medicine ward for further management and evaluation. On admission, a provisional diagnosis of insulinoma was kept and his abdominal ultrasonography was normal except for cholelithiasis of 6.6mm. Contrast enhanced CT scan of abdomen and pelvis did not reveal any mass lesion. An extended 75 g oral glucose tolerance test was performed which revealed a basal value of 72 mg/dl with peak at 1 hour of 174 mg/dl and lowest at fifth hour with a value of 38 mg/dl, with corresponding insulin value of >300 µIU/ml. Serum insulin antibodies were measured by enzyme linked Immunosorbent assay (ELISA) and were found to be >175 IU/ml and diagnosis of IAS was made. He was kept on a diet of frequent small meals and his symptoms gradually disappeared. Our patient was not found to have any autoimmune disease nor was he giving history of intake of any antidiabetic medication. On follow-up, he has not developed any episode of hypoglycemia again and has improved on dietary modification only.

## DISCUSSION

COVID-19 infection usually present with pneumonia and characteristic CT findings of ground glass opacities, so radiological investigations is an integral part of assessment and diagnosis of the COVID-19 infection.<sup>5</sup> The patient suffering from severe acute respiratory illness following COVID-19 infection and later presenting with extensive subcutaneous emphysema with evidence of

compression of airway in a COVID19 is not a very common finding in the medical literatures available apart from some case reports.<sup>2,6</sup> The most common causes for the extensive spontaneous subcutaneous emphysema may be explained by prolonged cough and aggressive disease pathology of COVID-19 infection. The pathophysiology mechanism were air leakage through the alveolar walls, damage by inflammation and damage by subsequent cytokine storm.<sup>7,8</sup> The chest X-ray shows air in the soft tissue space and prominent striations of the pectoralis muscle which gives an impression of Ginkgo leaf and hence the name of the sign as Ginkgo leaf sign.<sup>3</sup> Ideally the diagnosis of subcutaneous emphysema is done clinically by palpating the subcutaneous tissue which gives a crepitant feeling. Here, we report a case of insulin autoimmune syndrome which was suspected in our patient as he had very high serum insulin levels in association with hypoglycemia. EHH is characterized by excessive production of endogenous insulin that resulting in low blood sugar. Insulinoma is the most common cause of EHH. IAS is a rare cause of EHH, and very few cases have been reported worldwide. Majority of cases have been reported from Japan, a few cases have been reported in Caucasian population.<sup>8-11</sup> It may be associated with underlying autoimmune disorders such as Graves' disease, systemic lupus erythematosus, systemic sclerosis and rheumatoid arthritis.<sup>3,12</sup> Main cause of hypoglycemia in IAS is probably due to dissociation of insulin from its antibodies in the post-absorptive state. In this patient, 72 hour fast test did not cause hypoglycemia but it occurred spontaneously in the post-absorptive state 4-6 hours after meal. The widely accepted hypothesis for the mechanism of hypoglycemia in patients with IAS is that there is a mismatch between free insulin concentration and blood glucose due to insulin autoantibodies, which bind the hormone and release it later.<sup>13</sup> High levels of insulin (>300 µIU/ml) found in this patient also favoured a diagnosis of IAS. Majority of the cases of IAS occurs between the age group of 60-69 years in males and 30-39 years in females. Sex differences were not found except in the age group of 30-39 years where majority were found to be females.<sup>13</sup> Our patient diagnosed as IAS was a 67 year old male. He improved on dietary management alone consisting of frequent small meals. Acarbose has been used in the treatment of IAS as it decreases glucose absorption but its use is limited due to gastrointestinal side effects like bloating and diarrhoea. In refractory cases corticosteroids can be used. Insulin antibodies gradually decrease in many cases but the patients should be kept on a regular follow-up.<sup>14</sup> Our patient is on regular follow-up until the date he has been asymptomatic.

## CONCLUSION

IAS could be a rare cause of EHH in whom there is no any localize abdominal tumour and unable to explain the cause of extremely high insulin levels. As IAS mostly runs a benign course, unnecessary investigations and surgical procedures could be avoided. Insulin auto

antibodies should be tested in such patients in whom there is high index of suspicion. Thus IAS, though a rare cause of hypoglycemia, should not be missed.

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