Abstract
Hirata disease is a rare disease characterised by recurrent episodes of hypoglycaemia due to anti-insulin antibody. In most of these cases causative agents were sulphhydryl containing compounds like Penicillamine, Glutathione, and Methimazole. The presentation of disease closely mimics insulinoma. We report 52 years female patient presenting with recurrent episodes of hypoglycaemia due to anti-insulin antibody. On evaluation, underlying cause of antibody was found to be monoclonal gammopathy of unknown significance (MGUS).

Introduction
Hirata disease or insulin autoimmune disease (IAD) is a rare disorder, first case being detected in Japan by Hirata et al in 1970. Total 226 cases are reported from Japan, 10 from East Asia (non-Japanese) and 26 Caucasians. It mainly affects age group of 60-69 yr. It is characterised by history of exposure of sulfhydryl-containing compounds like penicillamine, glutathione, methimazole and alpha-mercaptopropionyl glycine. It has strong association with HLA-DR4. IAD was found to be third leading cause of spontaneous hypoglycaemia in Japan after Insulinoma and extra-pancreatic malignancy.

Case Report
52 year female presented with recurrent complaints of altered sensorium, confusion state, sweating, and palpitation not associated with chest pain and breathlessness since 2 days. There was no history of fever, convulsion, headache, nausea and vomiting.

Patient was admitted in private hospital and on evaluation she was found to be hypoglycaemic (blood sugar 23 mg%). Patient was administered Inj. Dextrose 25%, responded well and regained sensorium. But patient developed recurrent episodes (5 to 6) of symptomatic hypoglycaemia. Then patient was referred to our hospital for further management.

On inquiry, patient did not give history of oral hypoglycaemic agent or any other drug intake and yellow discoloration of sclera and urine. Personal and family history was unremarkable.

On examination, patient was afebrile, pulse 80/minute regular, and blood pressure was 112/74 mmHg. Central nervous system examination patient was conscious, oriented to time, place and person with no evidence of focal neurological deficit and neck rigidity. Rest of systemic examination was also normal.

Laboratory workup showed haemoglobin 11.5 gm%, total leucocyte count 7000/cumm, platelet count of 4 lac/cumm, SGOT 28 U/L, SGPT 8 U/L and serum creatinine 0.9 mg%. Electrolyte study revealed serum sodium 134 mEq/L, serum potassium 4.0 mEq/L, serum chloride 101 mEq/L serum calcium 8.7 mg% and serum phosphorus 3.6 mg%. Serology for HIV and hepatitis B and C was negative. Thyroid function test was normal.

As our patient was showing Whipple’s triad (symptoms of hypoglycaemia, documented evidence of low blood sugar and improvement in symptoms after glucose administration) suspecting Insulinoma we did 72 hour fasting test, which has sensitivity of 88.9% and a specificity of 100% for the diagnosis of insulinoma. At 6th hour of test, patient had symptomatic suggestive of hypoglycaemia, viz. sweating and palpititation, and blood sugar level was 38 mg%. Immediately sample for serum insulin and serum C-peptide levels were sent. Reports revealed serum insulin level 109.86 mU/L (Normal range: 3.0-25.0 mU/L) and serum C-peptide level 12.2 ng/ml (Normal range: 0.81-3.25 ng/ml). This was strongly suggestive of insulinoma.

In view of this imaging studies were done for localization of insulinoma. CT abdomen with triple phase contrast was normal and no pancreatic mass detected. CT scan has sensitivity of 82-94% for detection of insulinoma. Endoscopic USG was also normal. Endoscopic ultrasonography detects 77% of insulinomas in the pancreas. The yield can be higher if it is done in combination with CT scan. As CT scan and endoscopic USG was normal PET scan (using octreotide) was done which was also normal. It is thought to detect insulinoma in about half of patients.

As there was no evidence of Insulinoma, a possibility of extra-pancreatic malignancy leading to hypoglycaemia like hepatoma, adrenocortical carcinoma and carcinoids or anti-insulin antibody was suspected. Extra-pancreatic malignancies are characterised by high IGF-II level (as a cause of hypoglycaemia) and normal serum insulin and serum C-peptide...
levels ruling out these conditions in our patient and also imaging studies were normal. Therefore serum for anti-insulin antibody level was done and report was level of antibody >300 U/L (<12: Negative; 12-18: Borderline; >18: Positive).

In view of high anti-insulin antibody, serum protein for electrophoresis was done. Report showed presence of M band with location of band in gamma region. Serum immunoglobulin levels were as follows: IgA- 122 mg/dl, IgM- 169 mg/dl, IgG- 1230 mg/dl, Kappa- 1150 mg/dl, Lambda- 306 mg/dl (all within normal range). On immunofixation study cross-reactivity was seen with IgG Kappa.

Bone marrow aspiration report was: Normocellular, Erythrocytes 25%, Myelocytes + Metamyelocytes 35%, Plasma cells 3% which was essentially normal. Bone marrow biopsy showed Plasma cells 5 percent. Skeletal survey did not reveal any punched out lytic lesion. It was suggestive of monoclonal gammopathy of unknown significance (MGUS). It is observed that 1% per year of patients with MGUS go on to develop myeloma, all myelomas are preceded by MGUS.

Based upon all workup diagnosis of insulin autoimmune disease – Hirata disease due to monoclonal gammopathy of unknown significance was made. Patient was treated with tablet Voglibose 0.3 mg twice a day and advised annual serum protein electrophoresis with immunofixation study. After discharge, on tablet Voglibose, patient did not get hypoglycaemia during 1 month follow up.

Insulin autoimmune syndrome, Hirata disease, is most commonly seen in Asians. First case was described by Hirata et al in 1970. It is third most common cause of spontaneous hypoglycaemia in Japan after insulinoma and extra-pancreatic malignancy. The peak age of onset was 60-69 years for both sexes; there was no remarkable sex difference in the other age distributions except 20-29 year group, in which 77% were female patients with IAS. The duration of the transient and spontaneous hypoglycaemia was shown to be less than 1 month in approximately 30% of the patients, 1 to 3 months in 40% of the patients.

Diagnostic criteria include 1] high levels of total serum insulin, 2] Insulin auto-antibodies and 3] fasting hypoglycaemia.

Causes include 1] Graves’ disease on methimazole (MTZ) therapy, 2] Alpha mercaptopropionyl glycine (MPG) for hepatitis, dermatitis and cataract, 3] glutathione for urticaria, 4] Penicillamine for rheumatoid arthritis (all are sulphhydryl (-SH) containing drugs) and 5] benign monoclonal gammopathy.

Hirata disease has strong HLA association. HLA-DR4 is the dominant phenotype and DRB1*0406 is associated with the highest risk. Graves’ disease patients who developed IAS by MTZ therapy possessed a specific allelic combination, B62/Cw4/DR4 carrying DRB1*0406. Key step in pathogenesis is interaction between antigen-HLA-DRB1*0406 molecule-T cell.

Reducing compound such as MTZ, MPG, or glutathione cleave disulfide bonds of insulin in vivo. It causes exposure of self-antigens from insulin derived peptides and it gets attached to DRB1*0406 molecules on antigen presenting cells. It leads to proliferation of insulin-specific T cells.

This condition has led to novel concept of type VII hypersensitivity induced by the release of self-antigens from bound autoantibodies in serum. The self-antigens in type VII hypersensitivity are located in the liquid phase, unlike the self-antigens on the cell membranes in types II and IV hypersensitivities. Antibodies produced are monoclonal or polyclonal. Glutamate at position 74 in the HLA-DR4 B 1-chain was shown to be essential to the production of polyclonal insulin autoantibodies in IAS, whereas alanine at the same position of the HLA-DR B 1-chain might be important in the production of monoclonal insulin autoantibodies. IgG1 (γ/k) has low affinity constant and a large binding capacity, directed at a determinant at the asparagine site on insulin B-chain.

Figure 1 depicts the mechanism of hypoglycaemia in IAS. Beta stimulation by glucose causes release of endogenous insulin. This insulin binds with antibodies. As glucose level falls endogenous insulin release decreases. It is followed by release of bound insulin, not under control of blood glucose level, which precipitates hypoglycaemia.

More than 80% patients require no treatment and spontaneous remission is seen. In symptomatic individuals strategies used are stopping culprit drugs, change of food habits (small frequent meals), plasmapheresis to wash out antibodies from sera, use of alpha-glucosidase inhibitor to prevent post-prandial hyperglycaemia causing insulin peak levels and immunosuppression with steroids, azathioprine, or 6-mercaptopurine.

References