Insulin Autoimmune Syndrome (Hirata Disease)- Severe Hypoglycemic Episodes in Graves Hyperthyroidism Patient Treated with Methimazole

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Abstract: Insulin Autoimmune Syndrome (IAS) or Hirata disease is characterized by severe hypoglycemic episodes, a high level of immunoreactive insulin, and a high titer of insulin autoantibody in a person who has never received exogenous insulin. It is noted that IAS has a strong genetic predisposition and the majority of the IAS cases were reported from Japan where it is the third leading cause of hypoglycemia. It is also known that some drugs with sulfhydryl groups in their chemical structures can induce the formation of insulin autoantibodies in predisposed individuals, and Graves patient who possesses Bw62-Cw4-DR4 carrying DRB1-0406 maybe at risk of developing IAS when methimazole is administered. We present such a case which is very rare in our Caucasian population, who developed Hirata disease probably the first case in our Indian population.

Keyword: Hypoglycemia, insulin autoantibodies, Graves disease, Caucasian rarity

Our patient with Hirata disease
A 16 year old male from Melur near Madurai, studying 10th standard, presented to our department with complaints of polyphagia, significant weight loss of about 6kg, palpitation, hyper defecation for the past 6 months. No h/o. any headache or palpitation or defective vision. No h/o. cough with expectoration, fever, urinary disturbances including polyuria, bowel disturbances. No h/o. abdominal pain, vomiting. No h/o. weakness to move extremities or sensory disturbances including peripheral neuropathy. He gave a past h/o. primary complex at an age of 5 years, treated with anti-tuberculous drugs for 6 months.
He is not a known case of diabetes/HT/coronary artery disease/ COPD/asthmatic/epilepsy/thyroid disease He is a non-smoker, consumes mixed diet, non-alcoholic. He denies any chronic drug intake. No other family members suffer from similar illness. On examination, patient was conscious, oriented, afebrile, anaemic. No clubbing/cyanosis/pedal oedema/ significant lymphadenopathy. He had fine tremors. Examination of neck showed diffuse enlargement of both lobes of thyroid which were firm in consistency with a bruit heard and no cervical adenopathy. He had no ocular signs like proptosis with full range of ocular movements. He also had no pretibial myxoedema. Excessive sweating including both palms were noted. He had no features of vitiligo or other autoimmune features. His secondary sexual characteristics were present normally including axillary, pubic hair except for reduced moustache growth. His genital examination showed bilateral normal firm testicles with normal volume. He had low set ears with no marfanoid features. His pulse rate was 128/mt with a significant sleeping rate of 120/mt. His blood pressure was 160/70 in both upper limbs and 170/80 mm Hg in right lower limb, all recorded in supine posture. His height was 157cm, arm-span of 159cm and a body weight of 41kg. His BMI was 16.63.

Diffuse Thyroid enlargement

Cardiovascular system – S1S2 heard, no murmur, thyroid bruit heard Respiratory system- normal vesicular breath sounds heard with no added sounds Abdominal examination –not tender, Liver just palpable below right costal margin with a normal liver span, no splenomegaly, no free fluids CNS examination – fine tremors present. No focal neurological deficit, ocular movements full, no peripheral neuropathy

Investigation

Hb - 10.6 gm% TC - 7000 DC - P 63% L 35% E 02% ESR - 12 mm/hr Blood sugar - 96 mg/dl Blood urea- 33 mg/dl Creatinine - 0.8 mg/dl Sr.Na - 136 Sr. K - 3.8 Sr.Cl - 111 Total cholesterol – 93mg% Serum triglycerides – 88mg% Thyroid function test Total T3 - >800 ng/dl (70 – 204 ) Total T4 - 28.9 µg/dl (4.6 – 12.5) TSH - <0.01 µIU/ml (0.37 – 6.0) USG Thyroid – diffuse enlargement of both the lobes of thyroid ECG - Sinus tachycardia, no ST-T abnormalities Echo – normal LV ejection fraction of 62 percent with no regional wall motion abnormalities at rest He was diagnosed to have a primary hyperthyroidism/Graves disease and was started T.Methimazole 10 mg TDS,T.Propranolol 20 mg TDS, T.Rabeprazole 40 mg OD,T.Methylcobalamin 10 mg OD with advice to have frequent follow up. After 2 weeks, patient presented with 2 kg weight gain and improvement in tremor and palpitation with H/o recurrent episodes of intense headache, mild altered behavior and severe body pain. O/E Pulse - 80/min, BP - 120/80 mmHg Other system examination were normal A clinical diagnosis of tension headache/vascular headache was suspected CT brain - normal EEG - normal Routine Blood investigations – normal except for a random sugar value of 66mg% Thyroid function test
Total T3 - 466.47
Total T4 - 20.7
TSH - <0.01

He was advised to continue the anti thyroid drugs along with T.Sodium Valproate 200 mg BD, T.Amitriptyline 10 mg HS, T.Metaclopramide and T.Paracetamol

SOS Patient continued to have similar complaints and was brought at a midnight in a comatose stage with profuse sweating and cold peripheries during which a provisional diagnosis of hypoglycemic coma was made with a documented low sugar of 32 mg% and a full recovery after receiving intravenous 25% dextrose. During hospital stay (almost three weeks), an interesting phenomenon occurred. He suffered from severe hypoglycemic episodes almost everyday, mostly occurring between 3.00-5.00 am, although he took sufficient regular hospital meals. The hypoglycemic episodes were prevented by giving dextrose firstly by intravenous infusion or oral solution, and thereafter by dividing his meals into 6 times per day plus late supper with a total of 1700 calories/day, without any specific medication. Propranolol was stopped during hospital stay.

No more hypoglycemic episodes occurred about 4 days before the time of discharge. Fasting insulin assay - 145.85 mU/L (3.0 - 25.0) CT Abdomen with contrast - normal pancreas with no evidence of insulinoma C peptide assay was >7ng/ml (1.1-5 ng/ml) Anti microsomal antibody – titre 1/6400 Anti thyroglobulin antibody – Negative Insulin antibody >80 U/ml (<1U/ml) HLA typing - could not be done due lack of availability. He was diagnosed to have Insulin Autoimmune Syndrome (Hirata’s disease) and he was discharged with strong recommendation to divide his meals at least 6 times per day plus a late supper. Methimazole and propranolol were continued. Surprisingly, one month after discharge, he came again in an euthyroid state (clinically and laboratory). No more hypoglycemic episodes occurred, although he resumed his regular pattern of having three meals per day. Fasting and two hour postprandial blood sugar and fT4 levels were normal. fT4 - 1.77 ng/dL Total T3 - 2.18 ng/ml TSH - 0.004 µIU/ml Fasting Blood Sugar - 98 mg/dL 2h PP Blood Sugar - 112 mg/dL He is still on low dose methimazole with propranolol to-date and is on regular followup.

Discussion:
The reported case is a patient with newly diagnosed Graves’ hyperthyroidism, who had never been treated with antithyroid drug or received exogenous insulin. The first hypoglycemic episode occurred 14 days after treatment with methimazole was started. During admission, several severe hypoglycemic episodes occurred which were prevented by administering dextrose, and thereafter by dividing his meals into 6 times per day with a total intake of 1700 cal, without giving any specific medication. The hypoglycemic episode in this case did not occur in response to blood glucose changes or food intake, and can be classified as post-absorptive(fasting) hypoglycemia. Hyperinsulinemic hypoglycemia can be the result of hugs, critical illness, hormonal deficiencies, non-beta cell tumors, endogenous hyperinsulinism (including insulinoma, autoimmune process, etc.), or metabolic disorders of infancy and childhood. Underlying autoimmune disorders or exposure to specific drugs were presumed to be responsible for the development of insulin autoimmune syndrome. Some drugs have been reported to trigger autoantibody production in the syndrome, among others sulphhydryl drugs (such as methimazole, alphamercaptopropionyl glycine, and glutathione),
hydralazine, isoniazide, procainamide, and penicillin. Rarely, IAS may also result from monoclonal insulin-binding autoantibodies produced by multiple myeloma or benign monoclonal gammopathy.

Drugs containing sulfhydryl groups in their chemical structure can induce the formation of insulin antibodies in predisposed individuals. Of 190 Japanese patients with IAS, 42% received medication containing SH group, such as methimazole, alphamercuriopropionyl glycine, and glutathione. It is also known that patients with Graves' hyperthyroidism who were treated with methimazole are at high risk to have IAS. Methimazole is considered as a reducing agent, cleaving the disulfide bonds of insulin, and will be presented and recognized in the context of the DRB1*0406 gene product on the APC of Graves' patient. The possibility of insulinoma as the most prevalent cause of hypoglycemia had been considered in the diagnostic work-up of this case. However, the results of ultrasonography and CT-scan were normal (although negative findings do not definitely exclude insulinoma). Furthermore, to exclude the possibility of drug-induced hypoglycemia, methimazole and propranolol were temporarily discontinued for several days, but hypoglycemic episodes persisted. Insulin autoimmune syndrome is a quite rare condition and associated with a strong genetic predisposition. Since Hirata reported the first case of IAS in 1970, to date majority of the cases are Japanese, and only few cases are reported among caucasians/non-oriental ethnic groups. Uchigata et al showed that the HLA-DR4 allele, DRB 1*0406, is associated with increased susceptibility to IAS among Japanese, while DRB 1*0403 and DRB1*0407 are not. The extremely low prevalence of IAS among Caucasians can be explained by the low prevalence of DRB1*0406 in this population. Unfortunately we cannot support our case with a positive HLA typing for this patient due to lack of availability. Several other reports also came from outside Japan. In 1992, Burch et al reviewed 16 cases of IAS outside of Japan from different sources with various causes, besides his own case of IAS in a hypertensive patient treated with hydralazine. Cavaco et al (2001) reported two Portuguese with IAS who had different HLA-DR4 allele (subtype) and insulin autoantibody DRB1*0406 and a polyclonal antibody in a patient treated with penicillin, and DRB1*0403 and monoclonal antibody in a patient with 'idiopathic' IAS. Recently, Moreira et al. (2004) from Brazil reported a case of IAS in a Caucasian man, which may have been triggered by antibiotics. Ma et al (2005) from Taiwan reported a patient with pulmonary tuberculosis who developed IAS after treatment with antituberculous drugs, presumably isoniazid; unfortunately, no data on HLA typing were provided. It was hypothesized that inappropriate (non-regulated) release of autoantibody-bound insulin produces hypoglycemia. High levels of serum insulin probably may result from the dissociation of insulin from its antibodies, several hours after meals, when no further absorption of glucose is occurring (as cited by Dozio et al)(9) Hypoglycemia and the impairment of glucose metabolism occur as a result of a buffering effect of high levels of antibody on insulin bioavailability to target tissues and release of insulin from the circulating autoantibody pool is expected to be a function of the laws of equilibrium of mass action, and not in response to changes in blood glucose level. According to
Hirata, insulin antibodies peaked 2-3 months after the start of antithyroid treatment and then concentrations fell spontaneously even when methimazole was continued. After a year, hardly any insulin antibody could be found, even in previously positive cases.(1) In the majority (of the Japanese patients), no treatment was required, and spontaneous remission occurs within 6 months of onset.(1) In prolonged hypoglycemia and severe cases, IAS can be treated by plasmapheresis, immunosuppressive drugs, or by glucagon injection. Finally, the presence of sepsis that was resistant to several antibiotics contraindicated the use of high dose immunosuppressants.

Spontaneous remission was also observed in our case; he was in remission three months after methimazole, despite continuing that drug. No special treatment was given, except for dietary regulation. Based on the clinical course and laboratory findings, the reported case of ours except for HLA typing fulfilled the criteria of insulin autoimmune syndrome (Hirata's disease) in Graves' hyperthyroidism patient treated with methimazole. The evidences are as follows:

1). Clinical course: the patient was diagnosed with Graves' hyperthyroidism and was treated with methimazole, which was followed by severe post-absorptive (fasting) hypoglycemic episodes, which spontaneously remitted within 3 months after methimazole treatment was started;

2). Laboratory findings: high serum insulin, C-peptide, and insulin antibody levels (during hypoglycemic episode)

Conclusion

To the best of the author's knowledge, this is the first case of IAS reported from India. This case was of a South Indian young adolescent boy with Graves' hyperthyroidism, who fulfilled the necessary criteria for insulin autoimmune syndrome or Hirata's disease. Due to lack of availability, HLA typing cannot be done. Hypoglycemic episodes occurred after methimazole treatment. His serum insulin, C-peptide, and insulin antibody levels were high. He had not been treated with exogenous insulin before. During follow-up, he demonstrated spontaneous remission without any specific treatment despite still being on methimazole. IAS or Hirata's disease should be considered as the cause of hypoglycemia in Graves' patients treated with methimazole, particularly in Oriental Asian populations. To exclude insulinoma and avoid unnecessary invasive procedures, it is recommended to determine the insulin antibody in any case of hyperinsulinemic hypoglycemia.

References:


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