CASE REPORT

Autoimmune Hypoglycemia in Type 1 Diabetes Mellitus

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Background: Antibodies against exogenous insulin are common in type 1 diabetes mellitus patients. They can cause hypoglycemia, albeit uncommonly. **Case Characteristics:** A 14-year-old girl with type 1 diabetes mellitus presented with recurrent hypoglycemia. **Outcome:** High insulin, low C-peptide and raised insulin antibody levels documented during hypoglycemia. Plasmapheresis led to remission of hypoglycemia. **Message:** Antibodies to exogenous insulin should be considered as a cause of recurrent refractory hypoglycemia in type 1 diabetes mellitus patients.

Keywords: *Antibodies, C-peptide, Insulin therapy, Plasmapheresis*.

Hypoglycemia is a major problem in patients with diabetes mellitus, especially among those who are on insulin therapy. Autoimmune hypoglycemia is rare, and is caused by antibodies to either insulin or the insulin receptor. Patients who are on insulin often develop antibodies to the exogenous insulin but without any deleterious effect. The hypoglycemia due to antibodies to exogenous insulin was first described by Harwood in 1960 [1]. We report a case of immune-mediated hypoglycemia in a type 1 diabetes mellitus patient who had been on human insulin for five years.

CASE REPORT

A 14-year-old girl, known patient of type 1 diabetes mellitus since 9 years of age, presented with recurrent episodes of documented symptomatic hypoglycemia. She was on basal bolus insulin regimen with Neutral Protamine Hagedorn (NPH) and regular human insulin. The hypoglycemic episodes did not have any pattern and occurred both in fasting and postprandial state. These episodes were not preceded by any increased physical activity. On examination, she did not have any signs of insulin resistance like acanthosis nigricans. The insulin injection site did not show any lipoatrophy or hypertrophy. Her body mass index (BMI) was 19.8 kg/m^2. She was counseled regarding appropriate timing and adequacy of food intake. She was also taught the correct method of insulin injection technique, including how to take the correct dose in the insulin syringe. Despite these measures, hypoglycemia was persistent. Complete hemogram, renal function tests and liver function tests were normal. Other illnesses contributing to hypoglycemia like hypothyroidism, adrenal insufficiency and celiac disease were ruled out by appropriate investigations [Free T_4 1.19 ng/dL (Normal 0.89-1.76), TSH 2.81 µIU/mL (Normal 0.3-5.5), 8 AM Cortisol 11.04 µg/dL (Normal 3-18) Anti TTG antibody <4 U/mL].

Insulin injections were stopped for a week, but the hypoglycemic episodes still persisted. During one episode of hypoglycemia, her random blood glucose value measured by glucometer was 23 mg/100mL. At the same time, serum insulin was 94.4 µU/mL (2.6-24.9) and serum C-peptide was <0.3 ng/mL (1.1-4.4). Hypoglycemia with raised insulin and suppressed C-peptide could be due to the surreptitious use of exogenous insulin [2] or autoimmune hypoglycemia [3]. She was strictly monitored and ensured that she was not taking additional insulin. Insulin antibody levels by ELISA was 13 U/mL (Normal<12 U/mL). Insulin antibody studies by radio ligand assay was 6.8 mg/L (Normal 0-5) (research assay Addenbrooke's Hospital, Department of Immunology, Cambridge). In the presence of insulin binding antibodies the insulin assay would be highly unreliable, and hence polyethylene glycol precipitation studies were done which showed low insulin recovery further providing indirect evidence for the presence of insulin-binding antibody. Gel filtration chromatography studies done twice on patient's sample after incubating with insulin regular (Actrapid) showed the presence of high serum immunoreactivity against insulin. (***Web Fig.* 1** and **2**).

The diagnosis of autoimmune hypoglycemia was confirmed and she was started on prednisolone (1mg/kg/day). She did not respond to steroids, and hence four cycles of plasmapheresis were performed. From the second cycle, her hypoglycemic episodes stopped. She was kept in observation in our ward for one more week after the completion of the plasmapheresis to ensure that

she does not develop any hypoglycemic episode. Her repeat insulin antibody titer by ELISA one month after admission was 6 U/mL. She was discharged on basal bolus insulin regimen and for the past 18 months she is under our follow-up taking her usual regimen of insulin with no episode of hypoglycemia.

DISCUSSION

Antibodies to exogenous insulin, though common, rarely ever cause disturbances in glycemic control. These antibodies are commonly of IgG type, though IgE antibodies too have been described. The exact incidence of symptomatic hypoglycemia caused by the presence of antibodies to exogenous insulin is not known, with the published literature being in form of single case reports till now. Antibodies to insulin receptor may lead to a syndrome of extreme insulin resistance. These antibodies usually act as antagonist at the insulin receptor thereby causing insulin resistance and hyperglycemia. Rarely, these antibodies can act as agonist at the insulin receptor and cause symptomatic hypoglycemia [3]. Certain drugs like methimazole and alpha lipoic acid can also lead to the formation of antibodies to endogenous insulin in patients without prior exposure to exogenous insulin. When these antibodies to endogenous insulin cause symptomatic hypoglycemia it is called Hirata's disease or Insulin Autoimmune syndrome, occurring predominantly in Japan [3]. Symptomatic hypoglycemia in a 72-year-old male due to antibody to insulin precipitated by pantoprazole has been earlier reported from India [4]. Our patient was not on any drug other than insulin.

The mechanism by which these antibodies against exogenous insulin cause clinical symptoms depend on their binding characteristics. Antibodies with high binding capacity and low affinity, bind the insulin and release the insulin at odd times with no relation to food intake resulting in unpredictable episodes of hypoglycemia [5]. Treatment options include prednisolone, plasmapheresis, rituximab, mycophenolate mofetil and immunoglobulin infusion [6]. In conclusion, hypoglycemia in a diabetic patient on insulin needs a careful stepwise approach to diagnosis, and merely titrating the dose of insulin to avoid hypoglycemia might not be enough.

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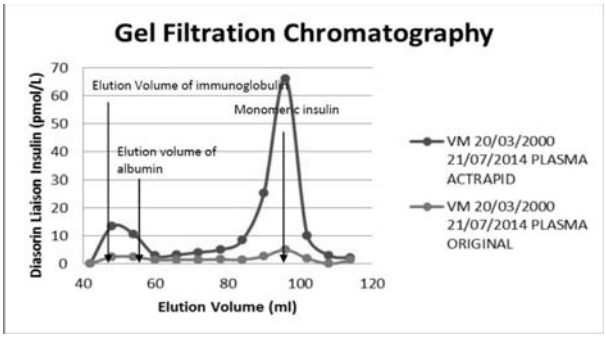
Errata

1. In the article entitled "Transcutaneous Bilirubin Nomogram for Healthy Term and Late Preterm Neonates in First 96 Hours of Life" published in Volume 54, May 2017, pages 369-372, and also for Webtable I, please read the unit of rate of rise in transcutaneous bilirubin as mg/dL/hour instead of mg/dL.

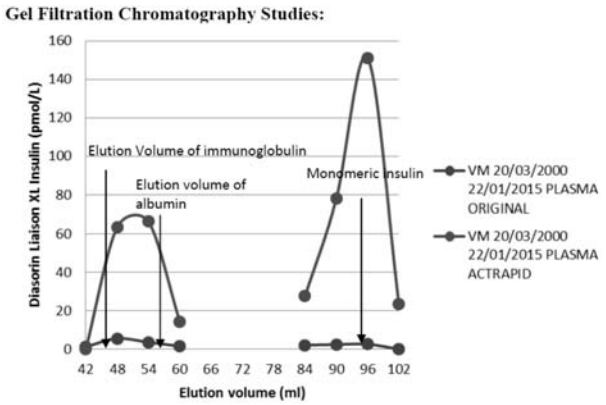
   REFERENCE

   Thakkar P, Chawda H, Doshi V. Transcutaneous bilirubin nomogram for healthy term and late preterm neonates in first 96 hours of life. Indian Pediatr. 2017; 54:369-72.

2. In the correspondence entitled "Hepatitis A with Superadded *Salmonella paratyphi* A Infection Presenting with Exudative Pleural Effusion and Acalculous Cholecystitis" published in Volume 54, June 2017, pages 514-515, please read the second author's name as "Payel Kundu".



WEB FIG. 1 *Gel filtration chromatography showing the presence of high molecular weight insulin immunoreactivity. The blue line shows the plasma of the patient without adding injection Actrapid. The red line shows the same after incubation with injection Actrapid. After adding injection Actrapid we can see the Immunoglobulin peak which having higher molecular weight is eluted first – hence the first peak and monomeric insulin having lesser molecular weight eluted later – hence the second peak. This demonstrates that the plasma has high molecular weight immunoreactivity against insulin.*



WEB FIG. 2 *Repeat chromatography studies confirming the persistence of insulin binding antibody.*