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Review Article

Two Cases of Spontaneous Hypoglycemia due to Insulin Autoantibody Syndrome – A Southern Indian Study

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ABSTRACT

IAS is a rare disease, characterized by hyperinsulinemic hypoglycaemia due to the development of autoantibodies against insulin, without prior treatment with insulin. Here we report two female cases of IAS, presenting in their 5th and 6th decades without prior exposure to any drugs that could induce antibody production. Both the patients were brought in unconscious state with a low blood sugar, ketonemia and demonstrated a high insulin levels in excess of 480 µIU/ml and demonstrable antibodies against insulin in the serum. Apart from genetic predisposition and the drugs that contain sulphydryl group, there could be other agents that induce this antibody production against insulin.

Keywords: Insulin Autoimmune Syndrome (IAS), Hypoglycaemia, Hyperinsulinemia, Insulin autoantibody.

INTRODUCTION

Insulin Autoimmune Syndrome (IAS) is a rare cause of hypoglycaemia, characterized by the production of autoantibody against insulin, in persons without prior administration of insulin. IAS was first reported in 1970 by Hirata et.al.(1), following which 244 cases have been reported throughout the world(2–4), among which more than 200 cases are reported only in Japan, where it represents the third leading cause of spontaneous hypoglycaemia(5) and about 30 cases are reported outside Japan, among which 1 case is reported from India(6). Uchigata et.al. identified specific HLA antigen strongly associated with IAS(7) and certain drugs such as methimazole containing sulphydryl group trigger this syndrome(7–12). Here we report two cases of spontaneous IAS among females presenting with hyperinsulinemic hypoglycaemia of unknown aetiology.

Case 1

A 53-year-old Indian woman was referred to our hospital with an episode of loss of consciousness yesterday for which she had been taken to a local hospital, wherein her blood sugar recorded was 46 mg/dl and administration of glucose restored her consciousness back to normal without any neurological deficit. One week prior to this episode she complained of dyspepsia, palpitation, tremors and giddiness with reduced appetite. There was no nausea, vomiting, headache, giddiness, double vision, tinnitus and blurring of vision. She is hypertensive for the last 3 years and is on regular medication with telmisartan 40mg/day and her blood pressure is often normal. There was no change in the anti hypertensive medication in the recent past nor she is using any OTC drugs. There was no past or family history of diabetes and similar complaints among the family members.

Her general and systemic examinations were unremarkable. Ketone bodies by dipstick method was 4 + and spot urine examination didn't reveal proteinuria and glycosuria. Plasma glucose was 53mg/dl and serum insulin was 480.5µIU/ml.

Insulinoma was suspected and she was investigated further. The serum Insulin to C-peptide molar ratio was >1. Ultrasonography of abdomen was normal and CT abdomen and pelvis didn't reveal any evidence of hyper enhancing lesion in and around the pancreas. Anti-TPO was slightly elevated, TSH, RA Factor, ANA and 8am serum Cortisol levels were normal. Her counter-

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regulatory hormones were normal and she was put on 72-hour fasting with a close monitoring of her clinical and biochemical parameters. The lowest documented plasma glucose was 50 mg/dl with persistent ketonuria, although she never reported symptoms of hypoglycaemia.

As CT abdomen and pelvis was taken and reported normal. Insulin and C-Peptide molar ratio was >1. A suspicion of IAS was kept in the background and she was investigated further. The anti-insulin antibody was positive, CECT abdomen, neck and chest was done to screen for neoplasms but were normal.

However to detect subclinical hypoglycaemia, a continuous ambulatory glucose monitoring was done by applying sensors. She advised to take frequent small feeds and to avoid spicy and fatty food stuff. She was discharged with an advice to take 20mg/day of prednesalone in the morning and to come for review after 3 weeks.

Case 2

A 67-year-old nondiabetic woman admitted to our hospital with an episode of loss of consciousness lasting for about 1 hour without convulsions, headache and head injury. One month prior to this episode she complained of palpitation, tremors and tiredness. There was no nausea, vomiting, headache, giddiness, double vision, tinnitus and blurring of vision. She is hypertensive for the last 5 years and is on regular treatment with amlodipine 5mg/day and her blood pressure is often within prescribed normal range. There was no change in the anti hypertensive medication in the recent past nor she is using any OTC drugs. There was no past or family history of IHD and COPD and similar complaints among the family members.

Her general and systemic examinations were unremarkable. Ketone bodies by dipstick method was 3+ and spot urine examination didn't reveal proteinuria and glycosuria. Plasma glucose of 28 and 43mg/dl, serum insulin was 1000 µIU/ml.

Insulinoma was suspected and she was investigated further. The serum Insulin to C-peptide molar ratio was >1. Ultrasonography of abdomen was normal and CT abdomen and pelvis didn't reveal any evidence of hyper enhancing lesion in and around the pancreas. Anti-TPO was slightly elevated, TSH, RA Factor and 8 am serum Cortisol were normal. ANA profile reported as Anti-Centromere B Antibodies strongly positive. Her counter-regulatory hormones were normal and she was put on 72-hour fasting with a close monitoring of her clinical and biochemical parameters. There was persistent ketonuria and she continued to have episodes of hypoglycaemia during the stay at the hospital.

As CT abdomen and pelvis were reported normal, Insulin and C-Peptide molar ratio was >1. A suspicion of IAS was kept in the background and she was investigated further. The anti-insulin antibody was positive, CECT abdomen, neck and chest were done to screen for neoplasms but were normal.

However, to detect subclinical hypoglycaemia, a continuous ambulatory glucose monitoring was done by applying sensors. She advised to take frequent small feeds and to avoid spicy and fatty food stuff. She was discharged with an advice to take 20mg/day of prednisolone in the morning and to come for review after 3 weeks.

Analyte	Case 1 Results	Case 2 Results	Reference Range
Plasma Glucose random	50	43	70-14 mg/dL
Urine Ketone bodies	++++	+++	Negative
Urine Protein	-	-	Negative
Urine Glucose	-	-	Negative
Serum Insulin	480.5	1000	2.6-24.9 µIU/ml
Serum C-peptide	2.42	3.34	1.1-4.4 ng/ml
Insulin/C-peptide molar ratio	4.1	6.2	<1
Insulin antibody	60 (Positive)	>100 (Positive)	<10 U/ml (Negative)
HbA1c	5.80%	6.00%	
Serum Cortisol morning	227	958.4	166-507 nmol/L
Serum Anti-TPO	52.18	24	Upto 34 IU/ml
Rheumatoid factor	8.5	10	Upto 14 IU/ml
ANA Profile	Negative	Anti-Centromere B Antibodies strongly positive.	
Serum protein electrophoresis	No Para-proteins detected	No Para-proteins detected	-
Liver function	Unremarkable	Unremarkable	-
Renal function	Unremarkable	Unremarkable	-
Thyroid Profile (T3, T4, TSH, fT4)	Within Normal limits	Within Normal limits	-
Serum electrolytes	Unremarkable	Unremarkable	-

Table 1: Laboratory investigations performed in our patient with Insulin Autoimmune Syndrome (IAS)

DISCUSSION

Here we report two cases of Insulin Autoimmune Syndrome (IAS) of unknown aetiology with a very high serum insulin and discord to levels of C-Peptide elevation, without history of diabetes mellitus or use of any medicines. These are possibly among few cases reported in the Indian population. Insulin autoimmune syndrome was first reported and has an ethnic preponderance in Japan(1–4). IAS is relatively common in Japan, where it is the third leading cause of hyperinsulinemic hypoglycaemia. Probably due to the high prevalence of HLA alleles that confer predisposition to this syndrome(13). It is thought that there is a strong association between specific HLA allele and IAS. Japanese IAS patients are DR4 positive in 96% of cases, possessing either DRB1*0406, DRB1*403 or DRB1*407 in polyclonal and DRB1*405 in monoclonal cases(5). But the prevalence of IAS among Indian nondiabetic population has not yet been reported.

The pathogenesis of IAS remains unclear, but the role of drug-induced autoimmunization has been suggested since drugs containing sulphydryl group (i.e. Thiamazole, Methimazole, D-Penicillamine or glutathione and Alpha Lipoic acid) induce the appearance of autoantibodies within few weeks after the beginning of treatment(4,14). Also, imipenem, penicillin G, and Beta-lactam antibiotics which generate sulphydryl groups have been recently implicated in the pathogenesis of IAS (15,16).

In addition to genetic predisposition, other acquired autoimmune abnormalities such as Grave's disease and pregnancy might promote the production of insulin auto antibodies(17). The 2nd case demonstrated strongly positive Anti-Centromere B antibodies, hence in-depth studies about the association between autoimmune disorders and IAS is needed.

IAS was suspected in these two cases because of the association of hypoglycaemia with extremely high levels of insulin. The hypoglycaemia probably results from the dissociation of insulin from its antibodies several hours after meals, when no further absorption of glucose is occurring during post prandial period(18). IAS must be considered in the differential diagnosis of hyperinsulinemic hypoglycaemia in order to avoid undue investigations and pancreatic surgery.

CONCLUSION

IAS although a rare disease to cause endogenous hyperinsulinemic hypoglycaemia, should be considered one among the differential diagnosis, apart from Insulinoma. Cases where CT couldn't localize any tumour and if patient demonstrates high levels of insulin with moderately raised proinsulin and C-Peptide levels with concurrent insulin to C-Peptide molar ratio of >1. Hence anti-insulin antibodies levels should be assayed in patients with high index of suspicion to avoid unnecessary investigations and unwarranted surgical procedures.

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