Case Report:

A rare case of autoimmune hypoglycaemia

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ABSTRACT

We report the rare case of a female who presented with episodes of spontaneous hypoglycaemia. Although she had high baseline insulin and C-peptide levels during the time she was symptomatic, she tested negative on hypoglycaemia provocation test with '72 hour extended fast'. Patient was later found to have very high titres of insulin antibodies suggestive of insulin antibody syndrome (IAS). She developed this autoimmune antibody response with no known triggering factor. Her symptoms subsided completely after a short course of oral corticosteroid treatment.

Key words: *Spontaneous hypoglycaemia, Insulin antibody syndrome*

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CASE REPORT

A 42-year-old female was admitted for evaluation of recurrent episodes of sweating with weakness. She reported symptoms of feeling hungry, tired and tremulous for nearly 6 months on more than 8 occasions. Most of her symptoms occurred late in the evening around 7 pm after her 'yoga' sessions. She reported good symptomatic relief of her hypoglycaemic symptoms with a carbohydrate snack.

She had amenorrhoea since eight years following delivery. She reports being investigated for the same and was told to have 'failed ovaries' the medical records of which were not available. In view of her pre-mature menopause, she was suggested to start hormone replacement therapy (HRT) using a combined oestrogen and progesterone preparation which she took from November 2014 to February 2016. She was also on supplementation with levothyroxine 125 mg/day for her primary hypothyroidism since her pregnancy. She did not have a history of diabetes mellitus nor was she living with anybody who was on treatment for diabetes mellitus.

She was admitted from the emergency unit after she presented with an episode of severe hypoglycaemia that involved neuroglycopenic symptoms such as giddiness, confusion, and altered sensorium. After admission, she was treated with intravenous (IV) dextrose and oral carbohydrate meal with which she recovered from the presenting illness. Given long standing and persisting symptoms leading up to hospitalisation, she was admitted and evaluated for spontaneous hypoglycaemia.

Serum anti-thyroperoxidase

On the day following admission, 8 AM fasting blood glucose (FBG) was 66 mg/dL with corresponding serum insulin of 2235.68 uIU/mL, C-peptide of 7.57 ng/mL (normal range - 0.78-5.19 ng/mL). On the same day, random blood glucose checked during the time she was symptomatic (in the evening around 7 PM) was 69 mg/dL with corresponding serum insulin of

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1571.54 uIU/mL, C-peptide of 5.66 ng/mL. Her serum thyroid stimulating hormone (TSH) and T3 were normal with (TPO) antibodies measuring 8033 µIU/mL (normal <9 µIU/mL). Her glycosylated haemoglobin level (HbA_{1C}) was 5.7% (high performance liquid chromatography method).

Given premature menopause following the last pregnancy, magnetic resonance imaging (MRI) of the brain with contrast was performed which showed focal well defined T1W hypo intense, T2W hyper intense lesion in the right and posterior aspect of the pituitary gland measuring 3x2.8 mm. There was no definite enhancement in contrast study. Posterior pituitary bright spot was visible. The infundibulum and bilateral parasellar regions and cavernous sinuses were reported to be normal. Cystic appearing focal lesion likely within the pars intermedia favoring a 'Rathkes cleft cyst' was identified.

Ultrasonography of the abdomen showed normal adrenals and renal shadows. A multiphase computerized tomography (CT) of the abdomen showed normal pancreas with normal calibre of main pancreatic duct. However, a prominent arterial branch arising from the posterior aspect of the splenic artery in the mid-body, leading to a small pinpoint region of blush in the pancreas measuring 2.3 mm was noted.

Given this finding, she underwent Ga68 DOTA Exendine PET-CT showed multiple nodules throughout the pancreas without CT evidence of the nodules (SUV 3.8; in the head of pancreas) suggestive of nesidioblastosis. (Figure 1) On day 4 following admission, FBG was 84 mg/dL with corresponding serum insulin of 225.49 µIU/mL, C-peptide was 4.44 ng/mL. Given multiple episodes of symptomatic hypoglycaemia in association with high serum Insulin levels at various times of the day both in fasting and post-prandial states, an "extended 72 hour fast" was performed, the results of which are tabulated below. (Table 1) Patient tolerated the fast well and needed no help to correct lower sugars that were observed during the fast.

Paired blood samples showed blood glucose 69 mg/dL and serum cortisol 25.37 μ_g/dL during the last day of the extended fast. In view of a negative result of a 72-hour extended fast for insulinoma, immunoglobulin G (I_gG) (enzyme linked immunosorbent assay) insulin antibodies were sent on last day of the test which showed a value >300 U/mL confirming the diagnosis of insulin autoimmune syndrome (IAS). Given the severity of her symptoms she was advised a course of oral prednisolone 0.5 mg/kg body weight for 4 weeks which was tapered over a course of a month and completely stopped. Her repeat I_gG insulin antibody level was 5.3 U/mL and she remains completely symptom free since on her follow-up visits till date.

DISCUSSION

Hyperinsulinemic hypoglycaemia due to autoantibodies to endogenous insulin in individuals without past exposure to exogenous insulin is referred to as IAS, or Hirata disease.[1] IAS is a rare cause of hypoglycaemia described in fourth decade with no predilection to either gender. It is most frequently seen in oriental nations, and is reported as being the third important cause of spontaneous hypoglycemia

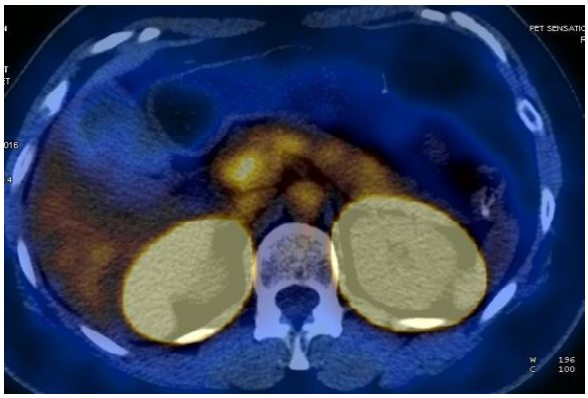

Figure 1: Ga68 DOTA Exendine PET-CT showing avid nodules throughout the pancreas - suggestive of diffuse nesidioblastosis. PET-CT=position emission tomography-computed tomography

Table 1

Date	Time (24 hr clock)	Blood glucose (mg/dL)	Serum insulin mIU/L	Serum C-peptide (ng/mL)
31/05/2016 (admitted in the evening)	20.19	83 (3 hours post prandial)	1571.26	4.81 ng/mL
72 hour extended fast started from post dinner 31/05/2016				
02/06/2016	6.18	69		
02/06/16	09.31	73		
02/06/2016	13.40	74		
02/06/2016	22.16	72		
03/06/2016	04.36	62	34.49	1.99
03/06/2016	07.37	69	44.37	2.70
03/06/2016	10.25	72		

in Japan following insulinoma and extrapancreatic neoplasms.[1] Most patients are known to present with both fasting and post-prandial hypoglycaemia, unlike patients with insulinoma who predominantly present with fasting hypoglycaemia.

IAS is seen to be higher in genetically predisposed individuals such as those with human leucocyte antigen (HLA)-DR4 Drugs, particularly those containing sulphydryl group (e.g., methimazole, carbimazole, isoniazid, imipenam, captopril) are well recognised triggers.[2] Precise pathophysiological basis of IAS remains unclear. Binding between the autoantibodies and insulin and subsequent hyperglycemia is thought to trigger the release of more endogenous insulin from pancreas creating pools of antibody bound insulin in the body. This large pool of antibody bound insulin molecules, when subsequently released at once inappropriate to the level of glucose is thought to trigger severe hypoglycaemia.[3]

Biochemically, IAS patients are found to have significantly higher insulin levels, generally above 1,000 pmol/L in sharp contrast to patients with insulinoma.[4] Another biochemical marker that could help distinguish these two disorders is Insulin to C-peptide ratio. Normally, insulin and C-peptide are secreted together from pancreatic beta cells in response to hyperglycemia in equimolar concentrations. Circulating half-life of insulin is about 5-10 minutes (predominantly metabolised by liver) compared to 30 minutes of C-peptide (predominantly metabolised by kidney) which makes normal insulin-C-peptide ratio less than 1. Whereas in IAS, this ratio changes to greater than one due to presence of large quantity of insulin molecules disproportionate to C-peptide.[5]

Our patient presented with repeated symptoms of hypoglycaemia and also had biochemically proven lower sugar values in keeping with her symptoms which were relieved with carbohydrate meal thus, satisfying definition of Whipple's triad that confirms 'a hypoglycaemic event'. When the prolonged fast was done to determine the role of β-cell polypeptides in the genesis of previously documented hypoglycaemia, although our patient had low blood glucose values, she never had values reaching lower than the accepted threshold of plasma glucose of 55 mg/dL or less.[6] The classic end-point of the prolonged fast has been the demonstration of Whipple's triad which did not occur in our patient thereby testing negative to this provocation. Simultaneously measured insulin and C-peptide levels were lower than they were before the beginning of the fast but, both her absolute insulin levels as well as insulin to c-peptide ratio throughout were keeping in with IAS more than insulinoma.

Concomitant presence of other autoimmune conditions such as Graves' disease, systemic

lupus erythematosis and other connective tissue diseases is well recognised.[7] Our patient had established autoimmune hypothyroidism and also premature gonadal failure which is presumed primarily due to ovarian antibodies or secondarily due to lymphocytic hypophysitis although; either of these diagnoses could be confirmed.

Radiologically, although CT abdomen with contrast raised a possibility of pancreatic focal lesion, PET showed diffuse nesidioblastosis keeping with increased physiological uptake by neuroendocrine tissue throughout the pancreas with no focal uptake that is expected in insulinoma.

Given autoimmune nature of the illness, more than three quarters of patients have spontaneous remission within 6 months of presentation. A report from a large series of cases from Japan showed spontaneous remission in about 82% of patients.[8] However, relief from symptoms of severe hypoglycaemia could be obtained from diet that includes small frequent meals low in carbohydrates. Reduced glycaemic load leading to reduced post-prandial peak is meant to minimise release of excess insulin thereby reducing the risk of symptomatic hyperglycaemia. Acarbose, an alpha-glucosidase inhibitor that delays carbohydrate absorption and reduces post-prandial hyperglycaemia has also been tried successfully in a few patients. Prednisolone 0.5-1mg/kg/day can be a useful adjuct.[9]

Although common in the orient, only one case has been reported so far from Indian sub-continent[10] that too in association with drugs that are known to trigger IAS. This is possibly the first case to be truly spontaneous IAS from India. It also illustrates the importance of step-wise approach to spontaneous hypoglycaemia that would lead to the correct diagnosis and treatment of this rare disease entity.

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