Case Report:

Varied presentation of hyperinsulinaemic hypoglycaemia

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ABSTRACT

Hypoglycaemia is a fairly common clinical entity, mainly due to its high prevalence as a complication of therapy for diabetes. Spontaneous hypoglycemia with unsuppressed plasma insulin is a relatively uncommon endocrine disorder. We are reporting three cases of hyperinslinemic hypoglycaemia due to insulinomas which include insulinoma presenting as seizures and abnormal behaviour in an adolescent boy, insulinoma presenting in the postpartum period and insulinoma developing in a woman with type 2 diabetes mellitus.

Key words: *Hypoglycaemia, Insulinoma, Hyperinsulinaemia*

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INTRODUCTION

Although hypoglycaemia in the setting of management of diabetes mellitus with insulin or oral hypoglycaemic drugs is common, spontaneous hypoglycaemia (i.e., hypoglycaemia unrelated to treatment with hypoglycaemic agents) is quite uncommon. In otherwise healthy individuals, such an event, occurring repeatedly is usually caused by an insulinoma, though rarely other aetiologies may be encountered, such as the presence of anti-insulin receptor antibodies or insulin binding antibodies. However surreptitious use of insulin or oral hypoglycaemic agents should always be considered. What is interesting about spontaneous hypoglycaemia also is its varied presentations and the multiplicity of settings in which it can occur. We present below a collection of our patients from a single centre, each of whom is unique in his or her own way and provides illustration of the protean manifestations and settings in which hypoglycaemia occurs.

CASE REPORTS

Patient 1

A 17-year old lean boy presented to the emergency department with recurrent attacks of loss of consciousness. These were previously diagnosed as seizures around one and a half years back, for which he had been commenced on maximum doses of phenytoin (400 mg/day). However the episodes of unconsciousness had remained uncontrolled. On evaluation in the emergency department he was found to be having low capillary blood glucose (25mg/dL). Hypoglycemia was corrected with 25% dextrose, following which he regained consciousness. Though he subsequently had recurrent attacks of hypoglycaemia requiring continuous dextrose infusion (up to 25 g/h), there was no recurrence of loss of consciousness. On hormonal testing, he had no evidence of hypothyroidism [thyroid stimulating hormone (TSH) was 5 µIU/L (normal 0.5-5.0), triiodothyronine (T_3) was 1.1 ng/mL (normal 0.8-2.0 ng/mL) and thyroxin (T_4) was 99 ng/mL (normal 55-135 ng/mL)] or adrenal insufficiency (serum cortisol collected at a venous plasma glucose of 25mg/dL was 25.6 µg/dL the normal response to hypoglycemia being cortisol > 18 µg/dL). Renal function and liver function tests were normal. Urine for ketone bodies was negative at the time of hypoglycaemia. Blood samples were collected during another episode of hyoglycemia for serum insulin levels. The insulin levels were inappropriately elevated (29.53 mU/L) at a plasma glucose level of 25 mg/dL. Computed tomography (CT) abdomen showed a mass of size 2×2 cm in the head of the pancreas, which enhanced with contrast. A magnetic resonance imaging (MRI) of the abdomen showed that the lesion was hypo-intense on T_1 and hyper-intense on T_2 weighted images. Intra-operative ultrasound showed a well defined hyper-echoic rounded lesion in the head of the pancreas. Central pancreatectomy was performed and the lesion was excised.

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Histopathology of excised tissue was consistent with insulinoma. Patient was hyperglyacemic for 2 days postoperatively, requiring insulin infusion. Subsequently he was euglycaemic on regular diet. Given the young age of the patient he was evaluated for the presence of the multiple endocrine neoplasia (MEN-1) and no evidence for the same was seen. His pituitary imaging was normal , prolactin was not elevated (4.9 ng/mL; normal = <25 ng/mL), growth hormone was suppressed after an oral glucose load (< 0.5 ng/mL) and the serum calcium was normal (9.8 mg/dL; normal = 8.8-10.4 mg/dL)

Patient 2

A 24-year old woman, presented 2 weeks postpartum, with episodes of sweating, dizziness, confusion and seizures. These episodes usually occurred in the early mornings. She was put on phenytoin for seizures. Later on, during work up for altered sensorium she was found to have hypoglycemia.

Her first documented capillary blood glucose was 36 mg/dL and she promptly responded to intravenous glucose administration. There was a history of similar, but less severe episodes (which required frequent feeding to avoid symptoms) in the first trimester. These symptoms were completely abolished during second and third trimester. Her liver function and renal function were normal. Her thyroid and adrenal function were normal (T3= 0.8ng/mL; T4 = 61 ng/mL, TSH = 2.8 µIU/ L and serum cortisol collected at plasma glucose of 40mg/dl was 19.3 µg/dL). Two hours after admission for a supervised 72 hour fast, she developed neuroglycopenic symptoms with plasma glucose of 40 mg/dl. Plasma samples collected at that time showed inappropriately elevated levels of serum insulin 6.43 mU/ L (normal = <3 mU/L), and C-peptide 0.96 ng/ml.

Based on the Mayo Clinic criteria,[1] endogenous hyperinsulinaemia was diagnosed. CT of the abdomen demonstrated a hypervascular (1 × 1 cm) lesion in the head of the pancreas. CT brain and electroencephalogram (EEG) were essentially normal. She underwent enucleation of tumor, with histopathology confirming an encapsulated islet cell tumor with positive immunostaining for insulin. She has remained euglycaemic following surgery.

Patient 3

A 72-year old lady with type 2 diabetes mellitus on oral metformin (500 mg/day) for the last two years was brought with recurrent attacks of confusion and altered behavior, more in the early hours of the morning for the past 1 month. There was no history of seizure activity or tongue bite. Patient would become normal on being administered oral sugar or after taking food. With the development of these symptoms she had stopped taking metformin. Following admission for evaluation, the lady had recurrent attacks of hypoglycaemia requiring dextrose infusions. On investigation, patient had normal renal, hepatic, thyroid and adrenal function. During a supervised 72 hours fast she became hypoglycaemic within half an hour with a plasma glucose of 50 mg/dl. Simultaneous insulin and C-peptide were elevated (24.42 mIU/ml and 2 ng/mL respectively). Spiral CT of the abdomen revealed a 2 × 1 cm lesion was seen in tail of the pancreas. Patient opted not to undergo surgery at that time and was therefore discharged.

DISCUSSION

Hypoglycaemia is a clinical syndrome with diverse causes in which low levels of plasma glucose eventually lead to neuroglycopenia. Insulinoma is a rare tumor, the incidence of which is estimated to be four cases per 1 million person-years. Insulinomas present with the neuroglycopenic and sympatho-adrenal symptoms induced by hypoglycaemia.[3] Recurrent confusional states are typical of insulinoma. Other symptoms include visual changes, unusual behaviour, palpitations, diaphoresis, and tremulousness.

Often diagnosed as refractory epilepsy, a significant proportion of patients receive aggressive and escalating pharmacotherapy with antiepileptics. Metabolic causes of seizures are often curable, but may be fatal if untreated. Patients 1 and 2 in our report were likewise being treated with antiepileptics. The critical importance of assessment of blood glucose level in patients with altered level of consciousness is again emphasized. Insulinoma,

though uncommon, is a potentially recognizable and curable disease, as long as there is a high index of suspicion. It should always be considered among the diagnostic possibilities in any patient with unusual or inexplicable neurological features, including atypical seizures refractory to pharmacotherapy. In one study, as many as 20% of patients had been misdiagnosed to be having a psychiatric illness, seizure, or other neurological disorder before the true diagnosis of insulinoma was made.[4]

A total of about 19 cases of insulinoma during pregnancy have been reported.[5] Most have presented in the first trimester. Only a single case of post-partum insulinoma has been reported previously, which presented a few hours after delivery.[6] Our patient (Patient 2) is unusual in presenting a few weeks post-partum. She had symptoms suggestive of hypoglycemia in the first trimester, which later resolved, only to reappear postpartum in a more severe form. Later pregnancy is known to be an insulin resistance state.[6] This may be due to placental counter-regulatory hormones like growth hormone variant, human placental lactogen, progesterone, and an increase in free cortisol levels.These factors may contribute to mask hypoglycemia in later stages of pregnancy.[6]

Patient 3 demonstrates that very rarely type 2 diabetes mellitus characterized by hyperglycaemia can morph into the opposite condition of hypoglycaemia following the development of an insulinoma. Insulinoma in patients with pre-existing diabetes is also extremely rare; indeed, the prevalence of prior diabetes amongst patients with insulinoma is much lower than that in the whole population (only 1 in 313).[7] There are sporadic case reports of insulinoma presenting in paients with both type 1 and 2 diabetes mellitus.[7-10] Interestingly, there is possibly an association between insulinoma and a family history of diabetes.[8] Recurrent hypoglycaemia in a diabetic, who is off insulin or oral hypoglycaemic agents, should raise the suspicion of this condition. The protean presentations and settings in which insulinoma occurs makes it a challenge to diagnose. A high index of suspicion and appropriate laboratory testing demonstrating the presence of inappropriately elevated insulin in the presence of documented hypoglycaemia is the key to successful diagnosis. This may be important as all manifestations of the disease and future complications can be avoided by surgical excision in these patients, which is ultimately curative.

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