Seizures Due to Insulinoma- A Rare but Treatable Cause

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Abstract
Hypoglycemia can cause multiple neuroglycopenic symptoms; seizures being one of them. Misdiagnosis and delay in treatment are common and prolonged hypoglycemia can lead to permanent neurological deficit or fatal coma. Hypoglycemia caused by an insulinoma is a readily treatable condition that should be considered in the differential diagnosis of intractable seizures. The following case report highlights the need for careful reassessment of all seizures that are atypical and refractory to medication.

Introduction
Insulinoma is the most common pancreatic islet cell tumors that arise from beta cells within the islets of Langerhans. The incidence is 4 cases per million per year.¹ They are uncommon, with female preponderance; the average age of presentation being fifth decade of life.² They are typically sporadic, solitary and less than 2 cm in diameter.³ The diagnosis relies on clinical features along with laboratory tests and imaging investigations to aid in localisation. We present a case of insulinoma in a 59 years old female who presented with history of recurrent seizures refractory to treatment with antiepileptic drugs.

Case Report
A 59 year old female patient presented to ER in unconscious state since early morning hours. For the last 4 years she was having recurrent fainting episodes on awakening in morning between 5 am to 7 am sometimes associated with abnormal posturing, perioral and eyelid twitching and unresponsiveness. The attacks would usually last from few minutes to about half an hour.

Patient was on antiepileptic drugs from last 4 years in view of recurrent seizures. The frequency of seizures had increased since last 5 months inspite of regular treatment. Patient also had complaints of headache, lethargy, diplopia, and blurred vision, particularly with exercise or fasting. She didn’t have history of fever, cough, breathlessness, weight loss or altered sleep pattern.

Patient was found to have hypoglycaemia (RBS- 48mg/dl) in ER. She was immediately managed with intravenous dextrose infusion after which she regained consciousness within few minutes.

Patient was not a diabetic, there was no significant past history of any illicit/prescribed drug usage. There was no previous history of any major illness or hospitalization or surgery. None of the family member was diabetic or suffering from any chronic illness.

General and systemic examination was unremarkable.

Routine investigations, ECG and cortisol levels were also normal.

Her capillary blood glucose was measured every 4 hours using a reflectance meter and in spite of i.v. dextrose infusion and normal oral feeds multiple episodes of hypoglycaemia were documented with RBS falling to as low as 30 mg/dl.

Patient’s serum insulin and c-peptide levels were checked. Her fasting plasma insulin level was 162.7 mU/L (Normal range 4.5- 40.5 mU/L) and c peptide level was 11.7 ng/ml (1.10 - 5.0 ng/dl) suggesting hypoglycaemia due to raised insulin levels and that too pancreatic origin.

Abdominal ultrasound and abdominal CECT (triple phase) scan revealed a small lesion in body of pancreas of approximately size 11*15 mm, thought to be solitary benign insulinoma (Figures 1 and 2). Patient was then taken up for surgery and underwent distal pancreatectomy. Macroscopic pictures of the distal pancreas with the tumor mass are depicted in Figure 3. Histopathology pictures of the insulinoma are shown in Figure 4. Postoperative period was uneventful and she was discharged in stable condition.

Discussion
Insulinomas which are typically a beta-cell tumor are the commonest hormone-secreting tumor of the gastrointestinal tract; the incidence is 4 cases / million / year. Tumors may occur as a unifocal sporadic event or in 5–10% of patients with MEN-1. 10% are metastatic, and a further 10% are multiple but behave as benign tumors. Insulinomas are found throughout the pancreas and are small (usually less than 20 mm). The median interval from onset of symptoms to the diagnosis of insulinoma is 2 years with a wide range of one month to 30 years as reported by Service F et al.¹

Many patients with an insulinoma are overtly well individuals and do not report the adrenergic symptoms of hypoglycaemia and present with neurological or psychiatric

Fig. 1: Triple phase CT abdomen showing the insulinoma (mass) of size 11*15 mm in the body of the pancreas and its relationship with the splenic artery and the superior mesentric artery

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manifestations that often lead to misdiagnosis. The delay in diagnosis is due to several factors. Firstly, the symptoms of insulinoma lack specificity, including various seizure disorders, personality change, bizarre behaviour, amnesia, convulsions, and incidentally dystonia and polyneuropathy; these symptoms are similar with many common neurological and psychiatric disorders. Secondly, fasting blood glucose level can be normal in some patients. Thirdly, hypoglycemia itself induces neuroglycopenic and autonomic unawareness.3,6

In a retrospective study with histologically confirmed islet cell adenomas, the interval between onset of symptoms ranged from one month to 30 years with the median of 24 months. A significant proportion (39%) were originally diagnosed with a seizure disorder. All these patients had symptoms of neuroglycopenia and three quarter reported relief of symptoms with ingestion of food.5

Insulinoma is one of the cause of post absorptive hypoglycemia also known as fasting hypoglycemia which occurs in non diabetic patients. Other causes being critical illnesses, hormonal (cortisol, growth hormone, glucagon or epinephrine) deficiency, alcohol consumption especially with empty stomach, other non islet cell tumors and certain medications. Diagnosis relies on key neuroglycopenic and sympathetic symptoms, blood glucose levels <50 mg /dl during monitored symptomatic episodes which improves with oral intake and a prolonged supervised fasting blood sugar test lasting upto 72 hrs. The above criteria along with increased c-peptide levels (>200 pmol/l), increased serum insulin level (>5 micromol/ml) in absence of sulfonylureas favoured a diagnosis of Insulinoma.4

Intraoperative palpation and ultrasound are the gold standard for localising an insulinoma with a reported success rate of 96 - 100%.7 MRI is said to be superior to CT for localisation of insulinoma among the non-invasive imaging modalities.

In Daggett and Nabarro’s review of 252 reported cases the most common neurological symptoms were confusion, coma, and seizures.3 Service FJ, Dale AJD, Elveback LR reported 12 % of 60 consecutive patients of insulinoma presenting with grand mal seizure.7

The risk of recurrence of insulinoma is greater among patients with MEN-1(21% at 10 and 20 yrs) than in those without MEN-1 (5% at 10 yrs and 7% at 20 yrs).2

Risk of post pancreatectomy diabetes after distal pancreatectomy is around 7.5% in patients without pancreatitis.9

Neuroglycopenia should be considered in all patients with seizures and other neuropsychiatric symptoms especially if they do not conform to diagnostic criteria or respond to standard treatment. Taking full history (including relationship of attacks to foods, non stereotyped or atypical attacks and poor response to antiepileptic treatment) and clinical suspicion are key to making a diagnosis of insulinoma. Once suspected, confirming the diagnosis with a seventy two hour fast is relatively simple.

Conclusion

This case emphasizes the importance of evaluating the metabolic cause of the refractory seizure disorder. The possibility of atypical causes like insulinoma associated seizures should be considered in patients with history suggestive of close relationship to food intake, history of weight gain, atypical attacks, seizures refractory to treatment. Early diagnosis and treatment can free many patients from recurrent unpleasant hypoglycaemic attacks which could be fatal and from burdensome multiple antiepileptic treatment.

References