Insulinoma masquerading as psychiatric illness

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ABSTRACT

Insulinoma is a rare neuro-endocrine tumour of Beta cells of islets of Langerhans of pancreas secreting excess insulin. 90% of tumours are benign, single or multiple, 5-15% are malignant. It is more common in females and usually occurs after age of 40. Symptoms are mostly because of hypoglycaemia. We present the case of insulinoma in a young girl, misdiagnosed as psychiatric illness and treated for the same for 3 years.

Introduction :

Insulinoma is a rare form of a neuroendocrine tumor of the pancreas that arises from beta cells of islets of Langerhans and secretes insulin. About 90% of insulinomas are benign single adenomas, 10% are multiple benign adenomas and 5-15% are malignant. Insulinomas occur more frequently in women than in men, with an average onset at about 45 years of age; most cases occur between30 and 70 years ofage.Insulinoma is uncommon after 80 years of age. 99% of insulinomas occur within the pancreas, rest 1% are mostly found in the wall of the duodenum orgastro-splenic omentum. Pancreatic insulinomas are usually average about 2 cm in diameter and appear with equal frequency in the head, body, and tail. Because of the nonspecific and insidious nature of the symptoms, which are mainly hypoglycemia related, the time between onset of symptoms and diagnosis is about 3 to 5years.

Case :

A 20 years old girl presented with the history of recurrent episodes of transient abnormal behavior since three years. The abnormal behavior had varied presentations such as -

1. Sudden onset unresponsiveness associated with a blank staring look but with maintained posture
2. Sudden onset violent tossing or writhing in the bed
3. Sudden crying without any reason, sometimes with irrelevant talk
4. Increased somnolence with 3-4 episodes of sleeping for about 12 hours at a stretch even during daytime

Each of the episode would last for about 20-60 minutes and in between the episodes she would be completely normal. There was no history of seizures. There was no history of any significant medical illness in the past and no history of psychiatric illness in any of the family members. She was treated as a c/o psychiatric illness with anti-psychotic medications by 2-3 psychiatrists during the past three years without any improvement even after regular treatment. CT Scan brain done 1 year ago on the advice of a psychiatrist was reported to be normal. In view of increase in the frequency & duration of episodes of abnormal behavior since 1 month in spite of regular psychiatric treatment, she was brought to our hospital & admitted in psychiatry ward.

On the second day of admission she developed three episodes of 'abnormal behavior' associated with sweating and blood sugars recorded during each episode were between 35- 45 mg/dl; Random blood sugar at the time of admission however was normal. The episodes were terminated after giving Intravenous dextrose. Patient was referred to medicine in view of low blood sugars and admitted in the MICU where 2 hourly sugar monitoring revealed at-least 3-4 readings below 50 mg/dl in 24 hours despite continuous maintenance therapy with intravenous dextrose. These readings were however associated with only a modest decrease in responsiveness or mild irritability i.e. the severity of

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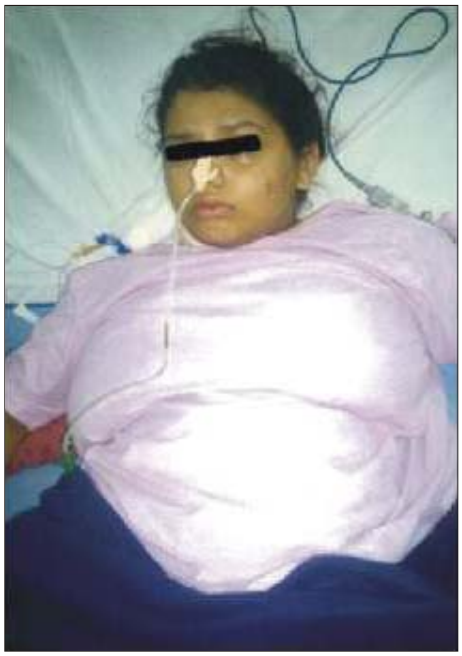


symptoms was quite mild as compared to the degree of hypoglycemia.

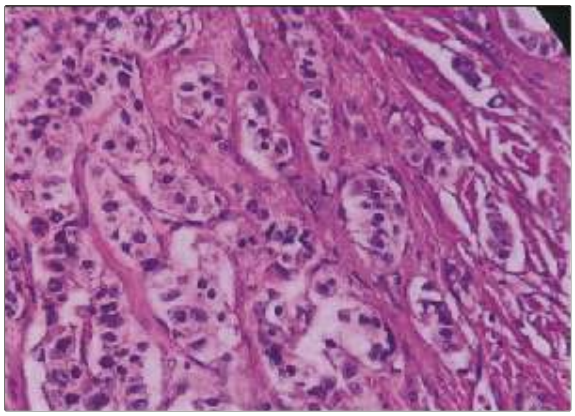
A detailed history was taken from her brother and mother after admission in MICU & repeated probing revealed that the episodes of abnormal behavior generally occurred early in the morning or following long intervals in between meals & always improved on being fed with something. Most of the episodes would be associated with profuse sweating. There was also history of weight gain of almost 25-30 kg over a period of three years because of repeated feeding. In view of the classical history & recurrent hypoglycemia fulfilling the criteria of Whipple's triad, she was evaluated for the underlying cause, most probably to beinsulinoma. So she was investigated further.

Investigations :

Patient's CBC, KFT, LFT, urine examination, X Ray chest, USG abdomen were within normal limits. Her fasting insulin levels were high - 41.90 IU/ml (normal value 2-25 IU/ml), C- peptide level was also high - 9.7ng/ml (normal value 0.8-4.2 ng/ml).

CECT Abdomen showed bulky head of pancreas (4.1 cm) and a relatively well defined, iso to hyperdense lesion with lobulated margins measuring 27 x 32 x 28 mm in dimensions was noted in the head of pancreas which was s/o insulinoma. In order to rule out MEN 1, MRI brain was done which revealed normal pituitary gland. Serum prolactin, Parathormone levels and ionic calcium levels were also normal.

After confirmation of diagnosis, patient was referred to surgery and underwent an enucleation surgery with removal of the tumor in to with the pancreas preserved completely. Histopathology of the tumor confirmed the diagnosis of insulinoma. Post-operatively her blood sugars remained in the normal range. Unfortunately patient developed sepsis 1 week after Surgery. Pancreatic leak was suspected as the cause of sepsis and was confirmed by ERCP. Stenting of the pancreatic duct was done. However while recovering from sepsis, patient developed aspiration pneumonitis and could not be revived.



Discussion :

Insulinoma is a rare form of a neuroendocrine tumor of the pancreas that is derived from the beta cells of islet of Langerhans and secretes insulin. About 90% of insulinomas are due to benign single adenomas, which average <2 cm in diameter; 10% are due to multiple benign adenomas. Approximately, 5-15% are malignant. 10% of insulinomas are associated with multiple endocrine neoplasia (MEN-I) in which case the tumor is more likely to be multiple and malignant and secretes additional hormones. Though insulinoma is common after 40 years of age, our patient was only 20 years old. Her tumour was 2.7 x 3.2 x 2.8 cm in size and was single, benign and

situated in the head of pancreas. Incidence of insulinoma is equal in head, body and tail of pancreas. There was no evidence of associated MEN1 syndrome clinically and on investigations in our patient. Symptoms of insulinoma are produced as the result of hypoglycemia; common initial symptoms are -confusion, weight gain, weakness, fatigue, headaches, faintness, altered mental state, altered behavior etc. Hypoglycemic episode can mimic disorders of awareness, epilepsy, transient ischemic attacks or psychosis and if untreated can result in cognitive impairment.[2]

In a retrospective study of 59 patients with histologically confirmed islet cell adenomas, the most common presenting diagnoses included neurological disorders (64%), especially seizure disorder (39%) while 8% patients were diagnosed as psychiatric disorder.

Because of their nonspecific nature and insidious onset, the time between onset of symptoms and diagnosis is about 3 to 5 years. This was exactly the case in our patient. For 3 years, she was diagnosed as a psychiatric case because of her abnormal behavior, hypoglycemia was not suspected and therefore not diagnosed. She had blank spells or violent behavior or excess sleepiness. Any young girl with abnormal behavior is considered as a psychiatric case usually, but detail history taking is mandatory for correct diagnosis. Especially association with prolonged fasting and sweating should have been given due significance. This caused delay in diagnosis and patient had to undergo unnecessary psychiatric treatment.

Frequency and / or severity of symptoms increases over time. Sometimes patients with insulinoma, similar to those with diabetes mellitus, can develop hypoglycemia unawareness, characterized by diminished symptoms, counter regulatory hormone responses, and β-adrenergic sensitivity, which are reversed after successful surgical cure .Thus, it is not uncommon for a patient with insulinoma with a plasma glucose concentration < 36 mg/dl to become completely asymptomatic thus delaying the diagnosis. This was also seen in our patient. Her symptoms were much less severe in proportion to her low blood sugar levels. Patients with MEN-I also can exhibit symptoms as a result of hypercalcemia and accompanying hyperparathyroidism or other excessive hormone secretions (islet production of ACTH, gastrin, and vasoactive intestinal peptide). Although insulinoma has long been classified as one of the so-called fasting hypoglycemia, such patients can experience hypoglycemia at any time of day, even 2 to 4 hours after a meal. Only about 25% of patients have hypoglycemia episodes solely after an overnight fast, and postprandial hypoglycemia has been reported to be the sole initial feature in most of the patients. Except in late-diagnosed malignant insulinoma cases in which an abdominal mass and signs of metastasis may be present, the physical examination is usually normal as was in our patient except weight gain. Suppression of normal β cells in islets by insulin released by the tumor can result in glucose intolerance or transient diabetes after removal of the tumor.

Diagnosis :

The diagnosis of insulinoma is readily established by the demonstration of fasting hypoglycemia (< 50 mg/dl; < 2.8 mm ol/l), inappropriately high plasma insulin (>5 μU/mL; >30 pm ol/L) and high C-peptide (>0.75 pg/mL; >0.25 nm ol/L) levels.

A plasma proinsulin concentration >5 pm ol/L can be useful if plasma insulin and C-peptide values are borderline; additionally, measurement of a high proinsulin-to-insulin ratio can be diagnostic. Our patient had high fasting insulin as well as C peptide levels. Proinsulin level measurement was not possible in our setup. The gold standard remains the classic 72-hour fasting test; 75% become hypoglycemic within 24 hours and up to 90% over 72 hours. Our patient became symptomatic in 12 hours of fasting. CT scan and MRI can detect large tumors and stage malignant ones but yield false positives and false negatives; these techniques correctly localize tumors only 50% to 70% of the time. In our patient, CECT abdomen revealed the tumor in head of pancreas. Preoperative transabdominal ultrasonography followed by intraoperative ultrasonography is considered the most sensitive and specific approach and has been

recommended for routine use; this approach along with palpation can be used to detect > 95% of tumors.

In patients who are suspected of having nesidioblastosis - although very rare in adults, the tests of choice are 18 F-DOPA PET scans and / or the selective calcium infusion procedure, because these tests will confirm the diagnosis of pancreatic hyperinsulinism as the probable cause of the hypoglycemia when reliable localization procedures are negative.

Treatment :

Surgery is the treatment of choice for insulinoma.[1] For patients with solitary adenomas, enucleation is curative; in cases that are thought to be due to a single adenoma, recurrence or lack of cure could be due to the presence of multiple adenomas. Our patient had solitary adenoma as per CECT abdomen report, therefore enucleation surgery was done. There was no need of partial Pancreatectomy. In 5% to 10% of patients, where the adenoma is not found; partial pancreatectomy can result in cure. Recurrence has been noted up to 18 years after the initial surgery. Recurrences are more common in patients with MEN-I (up to 20%). Multiple adenomas, hyperplasia, and malignancy require more extensive surgery.

The major complications of surgery, which include acute pancreatitis (13%), wound infection (11%), fistulas (9%), and pseudocysts (4%), are related to the extent of surgery. Unfortunately our patient developed postoperative septic complications and succumbed.

Commonly, transient hyperglycemia occurs and lasts up to 2 to 3 weeks because of suppression of normal islet function. Permanent diabetes mellitus can occur after partial pancreatectomy. Medical therapy is reserved for operated patients with recurrence who refuse another exploration and for those with inoperable malignant tumors. Diazoxide, which inhibits insulin secretion, has been used most widely. Approximately 60% (mainly those with benign disease) can be maintained nearly free of symptoms with only occasional hypoglycemia. The main side effects are fluid retention (≈15%) and hirsutism (≈5%); thiazide diuretics can be used to combat fluid retention and enhance hyperglycemic effects.

Malignant insulinomas respond poorly to chemotherapy.[1] Streptozotocin has been reported to reduce tumor size in about 50% of patients, with fewer than 20% achieving complete remission; although its use prolongs life, Streptozotocin has considerable renal, hepatic, and hematopoietic toxicity. The addition of fluorouracil has been reported to have advantages over streptozotocin alone. Mithramycin, doxorubicin (Adriamycin), and hepatic embolization have been tried with some success in refractory cases.

References :

1. Harrison's principles of internal medicine 19th edition :569, 2337.
2. Gupta M, Batra A, Hirve M, Chowdhary D et al. Paroxysmal dystonic choreoathetosis with symptomatic seizures secondary to hypoglycaemia caused by insulinoma. Ann Indian Acad Neurol 2011oct; 14 (4):313-5.doi;10.4103/0972-2327.91965.
3. Bhalla S, Punja V, Narang M, Kumari P, Gupta S.Seizures due to insulinoma-a rare but treatable cause. J Assoc physicians India 2017Mar; 65 (3):104-105.