

Case Report

Islets of hypoglycaemia: a rare case of adult onset nesidioblastosis

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ABSTRACT

A case of diffuse nesidioblastosis in an adult patient is reported in this study. A 24-year-old female with no known comorbidities presented with multiple episodes of documented recurrent hypoglycaemia and Hypoglycaemia induced seizures both in fasting and postprandial state. Her blood investigations revealed low plasma glucose levels, high insulin and C-peptide levels with positive 72-hour fast test. Her transabdominal USG and CECT abdomen did not reveal any abnormality, 68Ga DOTANOC PET CT done showed ill-defined diffuse somatostatin receptor expression in the pancreatic head and tail suggestive of nesidioblastosis. As patient was not willing for surgical treatment, hence started on medical treatment with oral nifedipine. Nesidioblastosis is very rare in adults. It is an important differential diagnosis in adults with hyperinsulinemic hypoglycemia although the incidence is very rare in adults. PET SCAN was used to non-invasively diagnose nesidioblastosis in this case. Surgery being the preferred choice of treatment in nesidioblastosis, there is limited data on medical line of management in nesidioblastosis.

Keywords: 68Ga DOTANOC, Hypoglycemia, Nesidioblastosis

INTRODUCTION

The term 'Nesidioblastosis' is gleaned from the Greek words nesidion meaning islet, and blastos meaning germ. Nesidioblastosis or diffuse hyperplasia of Islets was first described by George F Laidlaw in 1938 and is common cause of hypoglycaemia in infants.¹ Adult onset nesidioblastosis is rare, with the incidence of 0.3 case per million.² In adults, recurrent hypoglycaemia due to hyperinsulinemia is commonly caused by insulinoma. Some of the rarer causes like nesidioblastosis have been implicated in causing recurrent hypoglycaemia, and the first adult case of nesidioblastosis was described in 1975.³ Clinically, it is often difficult to distinguish nesidioblastosis from insulinoma. A case report of adult onset nesidioblastosis diagnosed noninvasively using 68Ga DOTANOC PET who was initiated on medical treatment, as the patient was not willing for surgery, which being the preferred treatment of choice.

CASE REPORT

A 24-year-old lady with no known comorbid conditions presented to the hospital with 2 episodes of generalized tonic clonic seizures with documented evidence of hypoglycaemia (grbs-40mg/dl), for which she was administered with intravenous 25% Dextrose, following which patient recovered completely without any deficits. Patient gives history of similar such episodes of recurrent seizures with documented hypoglycemic episodes since the past 2 years, for which patient was started on tablet Eptoin at an outside hospital. Patient had stopped taking those medications since past 2 weeks. She denies any history of usage of any medications, With no previous surgeries, no past history or family history of tuberculosis. On examination, patient was hemodynamically stable and systemic examination was clinically within normal limits. During the course in the hospital, Patient developed symptoms of hypoglycaemia (loss of consciousness, sweating and cold extremities)

with documented low GRBS (42 mg/dl) and improvement of symptoms on administering 25% dextrose. At this point, patient was educated to consume frequent meals and to watch for symptoms of hypoglycaemia with frequent blood sugar monitoring. Differential diagnosis at this stage included Addison's

disease, Insulinoma and non-insulinoma Pancreatogenous Hypoglycemic Syndrome. Initial investigations like serum electrolytes, thyroid function tests, serum calcium levels and MRI brain were within normal limits. Patient was worked up for hypoglycaemia according to (Figure 1).

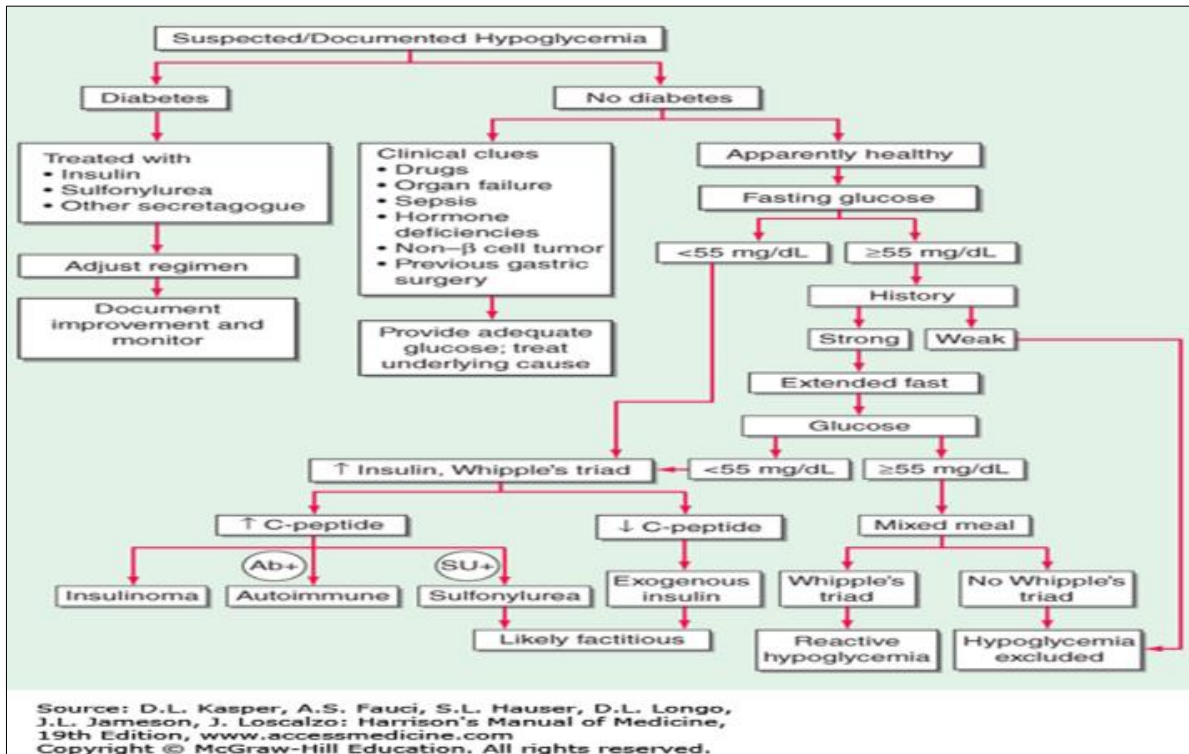


Figure 1: Algorithm for approach to hypoglycaemia.

Fasting Insulin levels and C-peptide levels were inappropriately elevated, with a positive 72-hour fast test. Based on these investigations and presence of Whipple's triad, a suspicion of Insulinoma was made. Ultrasound abdomen and pelvis and Contrast enhanced Computed Tomography (Figure 2) were done in order to localise Insulinoma. However, these investigations did not reveal any abnormality.

An endoscopic ultrasonography and FNA was then planned. Since patient did not give consent for this procedure, a review of literature was done to determine a non-invasive test to diagnose insulinoma. According to American journal of nuclear medicine and molecular imaging 2018, Gallium-68 DOTATATE PET/CT is an advanced functional imaging modality for non-invasive assessment of well-differentiated NETs.⁴ The sst2,3,5-specific radiotracer 68Ga-DOTANOC detected significantly more lesions than sst2-specific radiotracer 68Ga-DOTATATE in with GEP-NETs in a study by Wild D et al.⁵ A Ga68 DOTANOC PET CT was done, which showed ill-defined diffuse somatostatin receptor

expression in the pancreatic head and tail suggestive of nesidioblastosis (Figure 3).



Figure 2: Contrast enhanced CT abdomen showing pancreas with normal enhancement.

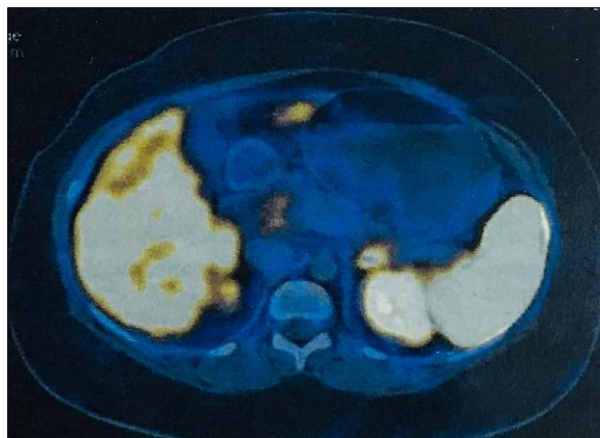


Figure 3: Ga68 DOTANOC PET CT image.

Diagnosis of nesidioblastosis was made based on symptoms of recurrent hypoglycemia with whipple's triad, evidence of endogenous hyperinsulinemia with a positive 72-hour fast test and functional imaging Ga68 DOTANOC PET CT (Figure 3) suggestive of nesidioblastosis. During hospital stay frequent blood sugar monitoring was done with frequent feeds, patient and attenders were also educated to identify symptoms of hypoglycaemia. Surgery is the treatment of choice.² As patient was not willing for surgery, she was initiated on medical therapy with tablet Nifedipine, a calcium channel blocker which was started at a dose of 20mg per day and then slowly escalated to 40mg per day. Patient tolerated medical therapy well with significant reduction in frequency of hypoglycemic episodes and seizures. Patient is in close follow up with the department of medicine and has been counselled regarding the need for definitive surgical treatment. Patient and attenders have also been educated regarding recognition of symptoms of hypoglycaemia and as to what measures have to be taken in such situations.

DISCUSSION

Nesidioblastosis is reported in infants as neof ormation of Langerhans islets from the pancreatic ductal epithelium, that results in hyperinsulinemic hypoglycaemia.⁶ However, in adults, hyperinsulinemic hypoglycemia is usually caused by insulinomas. Other causes like non-insulinoma pancreatogenous hypoglycemia syndrome and factitious hypoglycaemia are usually very rare and other possible etiologies of hyperinsulinemic hypoglycemia include drug induced hypoglycaemia, gastric dumping syndrome and exogenous insulin administration. The cause for adult-onset nesidioblastosis is usually unknown, although there are cases of nesidioblastosis reported following gastric bypass surgery.⁷ Insulinoma is the closest differential diagnosis for nesidioblastosis, and it is often difficult to clinically distinguish NIPHS from insulinoma. Clinically, NIPHS is characterized by postprandial hyperinsulinemic hypoglycemia, negative 72-h fast test, negative preoperative localization studies for insulinoma and positive selective arterial calcium

infusion tests. Histologically, diffuse islet hyperplasia with increased number and size of islet cells is present and confirms the diagnosis. The neuroendocrine cells of pancreas express high affinity somatostatin receptors (SSTR), 68-Ga DOTATATE specifically binds to the SSTR type II, which are highly concentrated in the pancreatic islet cells.⁹ Somatostatin receptor based imaging is the functional imaging of choice in diagnosis, recent guidelines have suggested use of SSTR PET should be the preferred imaging modality for initial diagnosis.⁸ Several studies have shown the high diagnostic accuracy of 68Ga-DOTATATE PET/CT in diagnosis of primary NETs compared with conventional imaging modalities.⁴ The sst2,3,5-specific radiotracer 68Ga-DOTANOC detected significantly more lesions than sst2-specific radiotracer 68Ga-DOTATATE in with GEP-NETs.⁵ A study using F18-fluoro-dihydroxyphenylalanine (F-DOPA) PET scan has been used to detect the hyper functional pancreatic islet tissue and to differentiate between focal and diffuse variants of nesidioblastosis with a reported accuracy of 96% in diagnosing focal or diffuse disease.^{10,11} In a study that compared 68Ga-DOTATATE PET/CT with gold standard pathology in diagnosis of Neuroendocrine tumours, the former had a sensitivity of 80-90% and a specificity of 82-90%.¹² Surgery is considered the treatment of choice for nesidioblastosis, distal or subtotal pancreatectomy is considered appropriate for nesidioblastosis as the risk of diabetes mellitus is less than 10% and a 70% success rate in symptom control.¹³ The extent of surgery is determined by Selective Arterial Calcium Stimulation Test (SACST). However, patient refused to undergo surgery. Hence a review of literature was done to look for the available options for medical therapy. Pharmacological therapy include use of diazoxide, acarbose, octreotide or calcium-channel antagonists. Diazoxide, a potassium channel blocker, was given in some patients who had recurrence of symptoms following surgery with some success, the prominent side effects being water retention, nausea, vomiting, dizziness, hirsutism and hypertrichosis.¹⁴ Acarbose has been used in patients with post gastric bypass hypoglycaemia with good success rate, but the role in adult onset nesidioblastosis is not well defined.¹⁵ Octreotide and pasreotide, the somatostatin analogues that suppress insulin secretion, have been tried in nesidioblastosis patients, and the former is used as a first-line therapy in cases where surgery is could not be done or not successful.¹⁶ Calcium channel blockers like verapamil, nifedipine and amlodipine are used in some patients with hyperinsulinemic hypoglycemia, since insulin release is a calcium dependent process and blockage of calcium channels can disrupt the insulin secretion from beta cells of pancreas. Hypotension, flushing and headache are the common side effects of calcium channel blockers. Patient was started on medical therapy with nifedipine, since nifedipine is reported to be useful in the management of nesidioblastosis in infants, initially started at a dose of 10mg per day sustained release formulation and slowly titrated to a final dose of 30 mg per day.^{17,18} Patient

initially experienced symptoms of giddiness, orthostatic hypotension, facial flushing and constipation. However, these side effects remitted substantially on use of medication for over a month. Since the start of treatment with nifedipine, patient has reported reduced frequency of hypoglycemic episodes and patient is completely alleviated of her hypoglycemic seizures. Patient is on treatment with nifedipine therapy since past 8 months, and is advised to monitor her blood sugars at home. After initiation of therapy, her blood sugars have not fallen below 60mg/dl. Her blood pressure is also monitored frequently including test for orthostatic hypotension. Diet remains the corner stone in management, aimed at reducing the stimulus for glycaemic spikes and insulin secretion. Dietary carbohydrate composition and food texture can also influence postprandial metabolism- a meal that lacks simple sugars but contains controlled portions of low glycaemic index carbohydrates consumed in multiple small meals and snacks containing up to 30 and 15 g respectively is usually well tolerated and often helpful in reducing hypoglycemic episodes.¹⁹ When symptomatic Hypoglycaemia develops patient is advised to use oral carbohydrates (10 to 15 g) to relieve symptoms and reverse downward excursions in glucose. If patient develops neuroglycopenic symptoms, family members are thought to administer injection glucagon or shifting the patient to nearby health care facility.

CONCLUSION

Adult-onset nesidioblastosis is a rare but an important cause of non-insulinoma hyperinsulinemic hypoglycaemia, and very few cases have been reported so far. In this case the diagnosis was made non-invasively by Ga68 DOTANOC PET CT. Surgery is considered the preferred treatment of choice and the available information regarding medical management is very limited. In this case patient was treated successfully with oral nifedipine.

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