

Successful Medical Treatment of Hyperinsulinemic Hypoglycemia in the Adult: A Case Report and Brief Literature Review

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Abstract

Hyperinsulinemic hypoglycemia is characterized by inappropriate insulin secretion from the pancreatic β cells causing low blood glucose levels. Nesidioblastosis is a very rare cause of hyperinsulinemic hypoglycemia in adults. Medical therapy can effectively improve disease symptoms. In 2014, a 45-year-old man presented with recurrent severe fasting and postprandial symptomatic hypoglycemia. The symptoms resolved after glucose ingestion. Fasting test was positive after only 4 h but imaging methods (abdominal computerized tomography, magnetic resonance imaging, endoscopic ultrasonography and octreotide scintigraphy) failed to identify pancreatic lesions. Hypoglycemia in face of endogenous hyperinsulinemia and lack of focal lesions in the pancreas in multiple imaging exams suggested the diagnosis of adult nesidioblastosis. The patient preferred conservative medical treatment in association with dietary recommendations. Nifedipine (30 mg/day) did not improve the glycaemic profile and was poorly tolerated by the patient. Diazoxide 150 mg/day was started, with progressive increase to 400 mg/day over 6 weeks. Patient has been successfully treated with medical treatment for 5 years, with no events of severe hypoglycemia, no significant side effects and with marked improvement in quality of life. This clinical case demonstrates that adult hyperinsulinemic hypoglycemia can be effectively controlled with medical treatment, which is a viable alternative to pancreatic surgery.

Keywords: Nesidioblastosis; Hyperinsulinemic hypoglycemia; Medical treatment; Diazoxide

Introduction

Hyperinsulinemic hypoglycemia (HH) comprises a group of clinically, genetically and histologically heterogeneous disor-

ders, characterized by inappropriate insulin secretion from the pancreatic β cells in the presence of low blood glucose (BG) levels [1]. In adults, 0.5-5% of hypoglycemias are due to HH [1]. The diagnosis of hypoglycemia is based on Whipple's triad (symptoms, signs or both consistent with hypoglycemia; a low reliably measured plasma glucose concentration (< 55 mg/dL) at the time of suspected hypoglycemia; resolution of symptoms or signs when hypoglycemia is corrected) [2]. Hypoglycemia may have multiple etiologies: insulinoma, post-bariatric surgery, adult-onset nesidioblastosis, autoimmunity, medications, non-islet cell tumors, hormonal deficiencies, critical illness and factitious hypoglycemia [3]. Insulinoma is the most common cause of endogenous HH in adults. On the contrary, nesidioblastosis is a very rare cause of HH in this age group and the etiology is still not fully understood [4]. This condition is a functional and anatomical disorder of non-neoplastic β cells characterized by hyperplasia, diffuse proliferation and hypertrophy of islet cells [5].

The majority of cases of adult-onset nesidioblastosis occurred after Roux-en-Y gastric bypass surgery and potential implicated mechanisms include: increased levels of incretins (glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide); improved β -cell sensitivity to GLP-1; absence of post-surgery reduction of islet cell mass/function; increased insulin sensitivity secondary to weight loss; inappropriate insulin hypersecretion and anomalous counter-regulatory hormonal response to hypoglycemia [6].

Nesidioblastosis is a possible cause of HH in individuals without previous history of bariatric surgery and negative localizing imaging studies. In this condition hypoglycemia usually arises in the postprandial period [3]. Treatment of nesidioblastosis includes the acute management of hypoglycemia and surgical or chronic medical treatment. Surgical treatment is the choice in patients with severe or refractory hypoglycemia. Prior to surgery, selective arterial calcium stimulation (SACST) should be done to determine whether the increased insulin secretion is focal or diffuse [7]. In cases where the imaging and functional tests fail to fully characterize the condition or the patient presents any contraindication to surgery, medical treatment can be considered. Long-term medical therapy comprises dietetic measures, alpha-glucosidase inhibitors, calcium channel blockers, diazoxide, and somatostatin analogues [1]. Dietary modifications might be sufficient to manage patients with mild postprandial hypoglycemic episodes [7, 8]. Treatment depends on the severity of hypoglycemic episodes. When medi-

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Table 1. Laboratory Tests

Parameter	Patient's 72-h fasting test	Endogenous hyperinsulinism [2]
Insulin ($\mu\text{U/mL}$)	6.4	≥ 3
Proinsulin (pmol/L)	5.6	≥ 5
C-peptide (nmol/L)	0.6	≥ 0.2
Beta-hydroxybutyrate (mmol/L)	≤ 2.7	≤ 2.7

cation is needed, diazoxide is the first-line medical therapy for long-term management [1].

We report a case of a 45-year-old man with HH, probably nesidioblastosis, successfully treated with medical therapy.

Case Report

We report the case of a 45-year-old man, referenced to the endocrinology department of a tertiary hospital in 2014 for investigation of severe and recurrent hypoglycemia. The patient was a construction worker, so these hypoglycemic episodes were life-threatening. He reported fasting and postprandial symptoms of dizziness, impaired concentration, profuse sweating, and peripheral tremor. After food ingestion, symptoms reverted. In one of such episodes capillary BG was confirmed to be below 40 mg/dL. Nevertheless, in routine blood analysis 2 years prior, he presented BG levels under 60 mg/dL, but no further investigation was conducted then. He denied recent significant weight gain. Medical history was notable for pulmonary tuberculosis in 2011, cured after a prolonged course of combined tuberculostatic drugs, as well as vena cava thrombosis, diagnosed in the same year and treated with acenocoumarol 4 mg/day since then. The patient denied previous surgical interventions, particularly bariatric or gastric procedures and previous diagnosis of diabetes or surreptitious intake of insulin or oral hypoglycemic agents. He admitted having regular moderate consumption of alcoholic beverages (48 g of alcohol per day). Physical examination was unremarkable.

Laboratory tests showed normal thyroid, adrenal and liver function. Liver ultrasonography was also normal. Glycated hemoglobin was 4.0% and ambulatory self-monitoring of capillary glucose confirmed low BG levels in fasting state (30 - 60 mg/dL) and postprandially (55 - 90 mg/dL), even after implementation of a low carbohydrate seven-meal diet plan. The 72-h fasting test led to the fulfillment of Whipple's triad after only 4 h (BG of 45 mg/dL). At that time, we documented elevated insulin, proinsulin and C-peptide and low beta-hydroxybutyrate (Table 1) [2], indicative of endogenous hyperinsulinism. Thirty minutes after glucagon administration plasma glucose rose to 79 mg/dL, increasing more than 25 mg/dL. Anti-insulin and insulin receptors antibodies were negative, as was also the test for detection of sulfonylureas. Insulinoma was suspected and imaging localization studies were requested. However, imaging studies, namely abdominal computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography and octreotide scintigraphy failed to identify pancreatic lesions.

Hypoglycemia in face of endogenous hyperinsulinemia

and lack of focal lesions in the pancreas in multiple imaging exams suggested the diagnosis of adult nesidioblastosis. The patient was hesitant toward any further invasive procedure as SACST and surgery. He opted for conservative medical treatment in association with dietary recommendations. A short trial with nifedipine 30 mg per day resulted in no amelioration of hypoglycemia and intolerable side effects of headache and peripheral edema. Treatment with diazoxide 150 mg/day was started, with progressive increase to 400 mg/day over 6 weeks. Patient now presents fasting glycemia of 78 - 86 mg/dL and 90 - 115 mg/dL postprandially. Blood pressure levels remain within normal range and the patient reports no diazoxide-related side effects. Patient has been successfully treated with diazoxide for 5 years with marked improvement in quality of life.

Discussion

Distinction between adult nesidioblastosis and an occult insulinoma can be difficult, due to the similarity of the biochemical profile and some overlap in clinical presentation. The main clinical feature of nesidioblastosis is postprandial hypoglycemia, although fasting hypoglycemia has also been reported, as is typical in patients with insulinoma [9, 10]. The definitive diagnosis relies on anatomical localization and histological examination of the pancreatic tissue [10, 11].

Nesidioblastosis is suspected in patients with HH and negative imaging studies, as we presented in this clinical case. Localization imaging studies comprise CT, MRI, transabdominal ultrasonography and somatostatin receptor scintigraphy, as well as more invasive studies (endoscopic ultrasonography and SACST) [3]. Besides, emerging GLP-1 receptor-based imaging with ^{68}Ga -DOTA-exendin-4 positron emission tomography-computed tomography (PET-CT) has been used for insulinoma localization in a few studies [12].

When these methods fail to identify a focal lesion, SACST with hepatic venous sampling is important to establish that the hyperinsulinemia has a pancreatic origin and its regionality within the pancreas [13]. This procedure can support nesidioblastosis diagnosis and guide surgical procedures in cases where pancreatic excision is considered [7]. In the clinical case presented, patient refused further invasive procedures and surgery. Considering patient's wishes as well as the risks involved in the catheterization procedure and pancreatic surgery, we decided for medical treatment.

The severity of hypoglycemia should guide the treatment. Dietary recommendations (reduction of free carbohydrate intake and fractionated carbohydrate intake throughout the day) can reduce postprandial glycemic excursions and fasting hypoglycemia.

mia and could be enough to treat cases of mild hypoglycemia [7, 8]. If dietary measures are not sufficient, pharmacological treatment with diazoxide, alpha-glucosidase inhibitors, calcium channel blockers or somatostatin analogues should be considered. Diazoxide is the standard medical treatment, inhibiting insulin secretion by opening the adenosine triphosphate (ATP)-dependent potassium channel of the pancreatic β cells, but its side effect profile can limit its use [14]. The more serious side effects are sodium and fluid retention leading to cardiac failure, diabetic ketoacidosis and nonketotic hyperosmolar coma, pulmonary hypertension, thrombocytopenia and neutropenia [14]. Non-serious side effects include hypertrichosis, anorexia, nausea and vomiting, and hyperuricemia [14]. Diazoxide is given orally as 3 - 8 mg/kg/day divided every 8 - 12 h [14, 15].

Somatostatin receptor (SSTR) ligands such as octreotide and lanreotide inhibit insulin secretion when given in high doses but may not be as effective as diazoxide [15]. The weak binding affinity and the limited range of SSTRs covered by these drugs impair their efficacy [16]. This therapy is a second-line option for refractory insulinomas and nesidioblastosis [16]. Pasireotide, a multi-SSTR ligand (SSRT 1, 2, 3 and 5), has been developed for the treatment of gastroenteropancreatic neuroendocrine tumors and there are a few reports of successfully long-term management of adult nesidioblastosis [17-19].

Insulin secretion is calcium dependent, thus calcium-channel blockade at the β -cell membrane can disrupt insulin release [20]. Calcium-channel blockers as verapamil, diltiazem and amlodipine may be used as potential therapeutic agents in cases of nesidioblastosis [20]. However, the use of first generation calcium antagonists (verapamil, nifedipine) may be limited by their side effect profile, including headache, flushing, bradycardia, and hypotension [20].

Alpha-glucosidase inhibitors, such as acarbose, delay the digestion of carbohydrates, resulting in lower BG concentrations after meals [21]. They have been successfully used in patients with post-bariatric surgery hypoglycemia, but its role in the management of adult-onset diffuse nesidioblastosis is not clearly established [21, 22].

In patients developing severe or refractory symptoms, surgical treatment might be required. When there is diffuse β -cell involvement, subtotal pancreatectomy is indicated, while in the focal type, partial pancreatectomy is the procedure of choice [23].

In the reported clinical case, we performed a trial with nifedipine, but this drug was poorly tolerated by the patient. He presented headache and peripheral edema without any improvement of hypoglycemia episodes. Medical treatment with diazoxide complemented with dietary recommendations re-established and maintained normoglycemia and a good quality of life for the patient for 5 years.

There are very few reports of medical treatment of HH in adults. This clinical case shows that adult HH can be successfully treated, with limited side effects, with diazoxide, which can be considered as an alternative to pancreatic surgery.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

VG collected the data and wrote the manuscript; FF was the endocrinologist in charge of the patient's care and reviewed the manuscript for important intellectual content.

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