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Case Report

A puzzling Case of Profound Hypoglycemia: Nesidioblastosis

Nathan M Lechien*

Clinical Education Director of Indiana University Indianapolis, USA

***Corresponding author:** Clinical Education Director of Indiana University Indianapolis, USA

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Abstract

Background/Objective: This case report is to describe the confusing scenario that can take place with a patient with undiagnosed nesidioblastosis.

Case Report: The patient in this case report undergoes multiple failed interventions before being diagnosed with her final diagnosis. The patient in which this case is written was diagnosed after multiple visits and inpatient stays.

Discussion: In addition to bringing this rare and misunderstood diagnosis to light, this case report describes the ill-defined diagnostic criteria for the disease and offers a solution proposed by another author.

Conclusion: The interest of a broad audience is of high importance due to the disease in question. As this is the case, the patient would have had less harm if a broader audience were to be knowledgeable on the topic. It is the hope of this case report to inform providers of the rare disease.

Keywords: Nesidioblastosis, Hypoglycemia, Refractory Hypoglycemia, Gastrectomy

Introduction

Nesidioblastosis is a term that originally described the neoformation of nesidioblasts, the cells that make up the Islets of Langerhans [1,2]. As such, the diagnosis can be described as islet cell hyperplasia. Diagnosis is characterized by histologic findings and should be considered in patients with recurrent and refractory hypoglycemia. Nesidioblastosis can be categorized under a further, broader term Non-Insulinoma Pancreas Autogenesis Hypoglycemia Syndrome (NIPHS). NIPHS is diagnosed through both clinical and biochemical findings. Nesidioblastosis is a rare disease that was first noted by George Laidlaw in 1938 [3]. The following case presents a patient with refractory and recurrent hypoglycemia. The patient struggled to find a diagnosis with functioning treatment.

Case Presentation

A 60-year-old female with refractory, recurrent, and profound hypoglycemia after gastrectomy and Nissen fundoplication. The patient has a history of insulin-independent Type II Diabetes Mellitus which was diagnosed after receiving glucocorticoids for an unrelated illness. She was treated as an outpatient with Metformin and Tresiba at the time. Following her diabetes diagnosis, the patient was seen for symptoms consistent with gastroparesis. Subsequently, she underwent multiple interventions including, Nissen Fundoplication x 2 and, ultimately, Roux-en-Y gastric bypass surgery. The patient's Tresiba and Metformin had to be discontinued after her gastrectomy due to labile blood sugars and a continuous glucose monitor was prescribed. A continuous glucose monitor was prescribed. Due to the stabilization of the patient's blood glucose over subsequent months, continuous glucose monitoring was stopped.

After the patient had been stable off anti-hyperglycemics for multiple months, the patient presented to the emergency room due to garbled speech and seizure-like activity. The patient's blood sugar was checked by EMS en route to the hospital and found to be 40mg/dL. This was initially treated with multiple ampoules of D50 in the field. In the emergency department, stabilization of her blood glucose level was obtained for a short time with ampoules

of D50 and continuous dextrose-containing intravenous fluids. Despite the patient being on multiple ampoules of D50 as needed, continuous D10 intravenously, and twice-per-day intravenous steroids, the patient's blood glucose levels continued to be labile. The patient's blood glucose levels were recorded many times lower than 40mg/dL. Exogenous and endogenous etiologies were ruled out during her admission including iatrogenic sources and self-harm. Additionally, radiologic studies were used to rule out insulinoma. The differential diagnosis during admission included sulfonylurea abuse, insulinoma, nesidioblastosis, and non-islet cell tumor. Despite a long course of intervention and diagnostic evaluation, no source for the patient's hypoglycemia was found. Diagnostic studies of insulin c-peptide, proinsulin, beta-hydroxybutyrate, cortisol, Insulin-Like Growth Factor (IGF) I, and IGF-II were still pending at the time of discharge. The patient was discharged home with low but stable blood glucose levels while on D50 ampoules as needed and a continuous glucose monitor.

The patient was instructed to follow up with an endocrinologist in the outpatient setting where further testing could be conducted to help identify an etiology. The endocrinology workup was largely unremarkable leading to a diagnosis of exclusion, insulin mismatch with carbohydrate intake. Unfortunately, the patient was not following a hypoglycemic diet at the time causing worsening symptoms and further hypoglycemia. She was referred to a dietitian for further instruction and education. The patient's hypoglycemic episodes slightly improved with these interventions. As such, the endocrinologist deferred any further work-up on the possibility of hyperinsulinism. Subsequently, the patient had a return of her symptoms and multiple hospitalizations due to hypoglycemic events. Throughout the care from our hospitalist team, further diagnostic studies were completed in both the inpatient and, later, in the outpatient settings. In the setting of continued hypoglycemic events, despite excellent adherence to a hypoglycemic diet, an outpatient endocrinologist ordered a mixed meal tolerance test to rule out a rare disease, Nesidioblastosis. The mixed meal tolerance test was incomplete and was not helpful in this case. Due to one of the suspected etiologies of the nesidioblastosis being the over-production of glucagon-like peptide-1 (GLP-1), the patient was started on dulaglutide, a GLP-1 receptor agonist. Unfortunately, the patient was unable to fill the prescription for Dulaglutide due to the medication being on backorder. At the time of data collection, the patient was still undergoing treatment for her hypoglycemia with as-needed D50 ampoules. The patient continues to be followed closely by an endocrinologist and her symptoms are becoming better controlled.

Unfortunately, the diagnosis of nesidioblastosis is a difficult diagnosis that requires both biochemical and histologic studies. Many patients will find that their care is complicated and interrupted due to multiple hypoglycemic events that lead to hospitalizations and evaluations by multiple different specialists to help elucidate an etiology. This particular patient has undergone a difficult disease course and her diagnosis is slowly coming to light due to the interruptions in care and diagnosis.

Discussion

According to the epidemiological survey conducted in Japan from 2017-2018, the prevalence of NIPHS was noted to be 0.09% per 100,000 adult population. In this study, 33 patients with NIPHS were identified but only 10 of them had nesidioblastosis that developed in adulthood.3 This is pertinent as nesidioblastosis found in young adults and children is categorized as a different disease state, Congenital Hyperinsulinism (CHI)/Persistent Hyperinsulinemic Hypoglycemia of infancy and childhood (PHH) [1-2]. The etiology of NIPHS is largely unknown. Although there are disease-causing mutations that are known for the genetically connected CHI/PHH, there has not been a connection to genetics for NIPHS in late-onset disease. Environmental causes have been proposed but not systematically investigated. Additionally, nesidioblastosis has been identified in a larger population of patients after gastric bypass surgery. After gastric bypass, an elevation in levels of GLP-1 is seen within the plasma [1,2]. This is since nutrients rapidly have contact with the location in which GLP-1-producing L cells reside, the distal ileum. As GLP-1 was shown in rodent studies to encourage β-cell proliferation, it was concluded that this could be the cause of the observed syndrome [1,2].

The determination of whether to work up a patient for this rare disorder hinges on the fact that more common etiologies are ruled out. An important differential included in patients such as this would be medication-related hypoglycemia, critically ill patients who may have sepsis, renal, hepatic, or cardiac failure as a source of hypoglycemia, hypothalamic, pituitary and/or adrenal insufficiency causing hormone deficiencies, and insulin-producing tumors. As nesidioblastosis is a morphologic and histologic term, the diagnostics rely on pathologic findings of a biopsy or surgical specimen. An argument arises in that these morphological findings are found in other disorders. In addition to this, some argue that the disease state may be a preliminary diagnosis where it may be easy to miss a small insulinoma. As diagnostic criteria seem to be argued, a literature review done in June 2023 proposed a well-thought-out standard clinical work-up that would help with the difficulties of this diagnosis:

1) Evaluation of general hypoglycemia symptoms and their situational occurrence (i.e., postprandial, fasting, spontaneous, exercise-induced)

2) Results of a 4 h (–6 h) Oral Glucose Tolerance Test (OGTT)

3) Results of a 72-h fasting test

4) Results of conventional imaging studies (CT, MRI)

5) Optional (might replace the next point in the future): results of functional imaging studies (where available, e.g., 68Ga-DOTA-Exendin-4 PET/CT or Somatostatin-receptor scintigraphy)

6) Selective Arterial Calcium Stimulation test (SACS) with proof of an insulin gradient (might also be useful to define the extent of pancreatic resection if surgery is planned)

7) Exclusion of other conditions (e.g., Hirata´s disease, insulin secretagogues, etc.) [1]

Subsequently, the criteria of the typical histologic findings of hypertrophic and or hyperplasia of pancreatic islets, enlarged and hyperchromatic nuclei, and neoformation of pancreatic islets from the duct epithelium should be used to establish a histopathological diagnosis [4]. This criterion allows for both biochemical and histopathologic findings to be considered in the diagnosis of nesidioblastosis. The mainstay of NIPHS treatment continues to be limited due to the lack of knowledge regarding this disease. A low-carbohydrate diet with a low glycemic index is initially suggested. This is to avoid strong insulin responses. Medication relies on a combination of α-glucosidase inhibitors, an ATP-sensitive potassium channel agonist (diazoxide), glucocorticoids, calcium channel blockers, and somatostatin analogs such as octreotide and pasireotide [1,2]. As a last resort, surgical intervention in the way of reversal of bypass or partial or subtotal/total pancreatectomy is offered to control symptoms.

Conclusion

Though the patient's endocrinologist suspected nesidioblastosis, the patient struggled to obtain an official diagnosis due to the many diagnostic requirements. This rare disease is coming more to light in the texts as authors strive to make its presence known. The diagnostic criteria put forth by Dieterle, et al. (2023) will make an easier path to diagnosis for patients with recurrent hypoglycemia and suspicion of nesidioblastosis. Treatment continued to be limited but can include a combination of medications to attack the disease process from multiple angles.

Key Points

1. Patients with refractory hypoglycemia should be initially checked for iatrogenic or self-harming causes along with radiologic studies to help in the diagnosis of potential insulinoma.

2. Nesidioblastosis should be considered in patients without evidence of the above.

3. There is not a well-described consensus for the diagnosis of nesidioblastosis but many argue that it requires both histologic and chemical evidence.

4. Treatment of NIPHS can include surgical and medical options but should be followed closely by an endocrinology specialist.

Acknowledgement

None.

Conflict of Interest

None.

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