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Case Report

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Noninsulinoma pancreatogenous hypoglycemia syndrome causing marked hypoglycemia in a cerebral palsy patient

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Abstract

Noninsulinoma Pancreatogenous Hypoglycemia Syndrome [NIPHS) is a rare disorder that often presents with postprandial hypoglycemia and neuroglycopenic symptoms such as seizures. In the setting of hypoglycemia with elevated insulin, workup includes, after ruling out exogenous causes, assessing for insulinoma as the most common cause of elevated insulin with hypoglycemia. Differntiation of NIPHS and insulinoma requires identification of hypoglycemial symptoms; fasting versus postprandial and negative localization imaging studies. This case highlights the presentation of NIPHS in a patient with cerebral palsy that manifested postprandial hypoglycemia, however underlying comorbidities delayed appreciation and diagnosis of hypoglycemic symptoms. Symptoms resolved after treatment with acarbose and reduced free carbohydrate intake was recommended as it has been reported to be beneficial in NIPHS.

Introduction

Noninsulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS) is a rare disorder that often presents with postprandial hypoglycemia and neuroglycopenic symptoms such as seizures. It is primarily differentiated from insulinoma in that there is a male predominance, symptoms are postprandial rather than fasting, as is typically the case in insulinoma, and localization studies are negative. We present a case of NIPHS causing severe hypoglycemia requiring multiple days of continuous 20% Dextrose infusion and brief continuous glucagon infusion. Presentation was further complicated as this was a female patient with cerebral palsy, and diagnosis was delayed due to her underlying comorbidities and difficulty appreciating the postprandial nature of her hypoglycemia episodes. Symptoms quickly improved post diagnosis and treatment with acarbose.

Case description

A 22-year-old female with past medical history of cerebral palsy (bedbound, nonverbal, and quadriplegic at baseline) presented to the hospital after being found unresponsive at home with decreased mentation. Per family, she had been lethargic for the past five days. They denied seizure activity or fevers. The family was not checking blood sugars; they did not have a blood glucose meter at home. Family history was unremarkable. Surgical history included a Percutaneous Endoscopic Gastrostomy (PEG) tube placed two years prior, which the family was using for administering tube feeds. Vitals were unremarkable. Other than typical features of cerebral palsy, such as abnormal posture, muscle spasticity, and hyperreflexia, physical exam showed decreased mentation from baseline as the patient was not opening eyes. A complete blood count was normal. The basic metabolic panel was also within normal limits, other than a mildly decreased blood glucose of 72 mg/dl. Subsequent infectious workup was negative. The decision was made to resume home tube feeds at a reduced rate through her PEG tube as mentation began to improve throughout the night. The subsequent morning, the patient's blood sugar significantly dropped to 66 mg/dl. Tube feed rate was increased at that time; however, blood glucose further declined to 42 mg/dl a few hours later. Over the next few days, she required increasing amounts of continuous dextrose infusions up to 20%. Tube feed rates were

concurrently increased and switched to high carbohydrate formulas with no improvement in blood glucose. The patient was also given a continuous glucagon infusion with minimal benefit. Further workup revealed normal levels of insulin at 24.7 uIU/ml and decreased levels of proinsulin and c peptide at 16.8 pmol/L and 7.4 ng/ml, respectively. Insulin antibody test was also negative. Differential shifted towards insulinoma versus NIPHS, with subsequent ultrasound and CT abdominal imaging negative for lesions or tumors in the pancreas. No other acute pathology was noted. Considering these findings, acarbose was initiated with dramatic improvement in hypoglycemia. The patient was discharged home with that medication at baseline mentation.

Discussion

This case was complicated in that hypoglycemia and neuroglycopenic symptoms were difficult to appreciate, considering the patient's nonverbal status secondary to cerebral palsy. Under normal physiological conditions, the body responds to the introduction of glucose with precisely calculated insulin secretion via the pancreatic β-cells. To prevent hypoglycemia, insulin secretion is reduced as glucose levels fall [2]. Fail-safe counter-regulatory mechanisms exist to increase glucose in the setting of severely low levels. In the acute setting, glucagon and epinephrine are released, while cortisol and growth hormone are activated in a delayed manner to increase glucose. Failure of insulin secretion to be blunted despite these mechanisms suppresses glycogenolysis and gluconeogenesis [3,4]. In the absence of glucose production, postprandial hypoglycemia is a risk.

Hypoglycemia can present with adrenergic symptoms such as tremors, anxiety, palpitations, and sweating at plasma glucose level at or below 3.3 mmol/L. Another aspect of postprandial hypoglycemia that was difficult to ascertain in this patient but has been known to present are neuroglycopenic symptoms. These consist of a range of concerns, including lightheadedness, vision changes, altered cognition, seizures, and coma. These findings are seen with plasma glucose level at or below 2.7 mmol/L and are correlated with cerebral glucose deprivation [5].

Symptoms of hypoglycemia in the setting of inappropriately elevated insulin have to be investigated. Insulinomas, NIPHS, insulin autoimmunity, congenital endogenous hyperinsulinemia, fructose intolerance, and exogenous consumption are part of the differential diagnosis [6]. Sulfonylureas and meglitinides are medications that upregulate insulin secretion, resulting in elevated plasma insulin, c-peptide, and proinsulin levels. If a drug screen is negative and exogenous causes have been ruled out, the most common cause of endogenous hyperinsulinemia hypoglycemia is due to insulinomas. These individuals tend to present with fasting hypoglycemia, and 98% of the time have a tumor that is localized preoperatively with imaging studies and perioperatively with ultrasound and exploration [1]. Although some studies have shown that there are rare cases reported of insulinomas with postprandial symptoms, in the absence of imaging findings, postprandial hypoglycemia is associated with NIPHS. NIPHS has biochemical findings similar to insulinomas on workup, including elevated plasma insulin, C-peptide, and proinsulin with low beta-hydroxybutyrate. Studies on patients worked up for NIPHS have shown positive arterial calcium stimulation tests, indicating increased pancreatic β-cell function. Biopsy of pancreatic tissue showed β-cell hypertrophy and nesidioblastosis without evidence of insulinoma or mutation of Kir6.2 and SUR1 [7].

After diagnosis, management of NIPHS depends on the severity of symptoms. For mild to moderate symptoms, dietary modification, including reduction in free carbohydrate intake and spacing of carbohydrate intake, can improve glycemic excursions. Foods with complex carbohydrates and low glycemic index are recommended over foods that are simple carbohydrates with high glycemic index. With persistent symptoms, a first-line drug that is prescribed is acarbose. An α-glucosidase inhibitor, acarbose slows the breakdown of complex carbohydrates to glucose thus reducing the insulin surge. Other therapies include diazoxide and octreotide, which has been seen in case reports to reduce insulin secretion. For diazoxide, it inhibits insulin secretion from pancreatic β-cells by acting on ATP-sensitive potassium channels, whilst octreotide binds to somatostatin receptors on pancreatic and inhibits calcium influx [8,9]. In the case of severe symptoms or NIPHS refractory to medical management, partial or subtotal pancreatectomy has been shown to improve symptoms in a majority of patients.

In the setting of this case, postprandial symptoms were difficult to ascertain, given that the patient was being administered continuous tube feeds through her PEG tube. Looking back, the worsening of the hypoglycemia right after tube feeds were initiated was characteristic of NIPHS.

If the diagnosis of NIPHS had been made sooner, a prolonged hospital stay with varying infusions of dextrose and glucagon could have been avoided. Paradoxically, increasing tube feed rate and changing formula to higher carbohydrate content in the hope of ameliorating hypoglycemia may have worsened the issue as reduced free carbohydrate intake has been reported to be beneficial in NIPHS. In cases of severe hypoglycemia, physicians should have a high index of suspicion for NIPHS. Medications such as acarbose can be particularly helpful in such scenarios.

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