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Case Report

Noninsulinoma Pancreatogenous Hypoglycemia Syndrome in a Patient With 1p36 Deletion Syndrome

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Abstract

The 1p36 deletion syndrome involves a phenotypic presentation that includes central nervous system, cardiac, and craniofacial anomalies. We report the case of a 21-year-old female patient with 1p36 deletion syndrome who was found to have noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) after hospitalization for persistent falls. On admission, vital signs were normal and physical examination revealed a thin, nonverbal patient. During hospitalization and prolonged fasting (14-18 hours), she persistently developed hypoglycemia (serum glucose nadir 57 mg/dL [3.2 mmol/L] [70-100 mg/dL; 3.9-5.6 mmol/L]). Subjective symptoms of hypoglycemia were not confirmed due to patient's cognitive impairment. Hypoglycemic events continued despite feeding and dextrose-containing fluids. Further workup included a critical sample that revealed a serum glucose 59 mg/dL (3.3 mmol/L), insulin 20.6 μIU/mL (123.6 pmol/L [5-15 μIU/mL; 30.0-90 pmol/L]), proinsulin 33 pmol/L (3.6-22 pmol/L), C-peptide 1.74 ng/mL (0.58 nmol/L [0.8-3.85 ng/mL; 0.27-1.28 nmol/L]) and beta-hydroxybutyrate < 1.04 mg/dL (< 0.10 mmol/L; [< 4.2 mg/dL; < 0.4 mmol/L]). Insulin antibodies were negative. After confirmed insulin-mediated hypoglycemia, imaging studies followed. Pancreatic protocol abdominal computed tomography (CT), Ga-68 DOTATATE PET/CT scan, and endoscopic ultrasound found no pancreatic mass. Selective arterial calcium stimulation test showed a two-fold increase in insulin levels in 3/3 catheterized pancreatic territories. The patient started octreotide injections with resolution of hypoglycemia and was discharged on monthly lanreotide injections. To our knowledge, this is the first case reported of noninsulinoma pancreatogenous hypoglycemia in a patient with 1p36 deletion syndrome.

Key Words: 1p36 deletion syndrome, nesidioblastosis, hypoglycemia, hyperinsulinism

Abbreviations: CT, computed tomography; Mb, megabases; NIPHS, noninsulinoma pancreatogenous hypoglycemia syndrome.

Introduction

Chromosomal 1p36 deletion syndrome impacts 1 in 5000 newborns and comprises a heterogeneous phenotypic syndrome. Spanning 30 megabases (Mb), chromosome 1p36 includes many genes and can present in a variety of pathologies. First described in the 1980s, phenotypic presentation is now known to include developmental delay, intellectual disability, neuropsychiatric disease, seizures, brain anomalies, vision loss, hearing loss, cardiomyopathy, left ventricular noncompaction, congenital heart defects, short stature, cleft palate, and/or craniofacial anomalies [1]. This syndrome is usually diagnosed in childhood, with a reported 6.12 years mean age at diagnosis [2]. To our knowledge, no reports of hypoglycemia have been reported in this syndrome. Nesidioblastosis, or noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), is a rare diffuse pancreatic hypertrophy with subsequent hyperinsulinemic hypoglycemia. Current understanding of this phenomenon describes it as pathologic budding and differentiation of pancreatic epithelial cells into β islet cells, creating a broad overgrowth of the pancreas resulting in a ductulo-insular complex seen on histology. This may be genetic, iatrogenic, or environmental in etiology [3–5]. Persistent hyperinsulinemic hypoglycemia, the hallmark of NIPHS, is caused by an insulinoma or NIPHS. Therefore, diagnosis requires serologic workup consistent with endogenous hyperinsulinemic hypoglycemia followed by imaging studies. If imaging fails to identify a pancreatic mass, selective arterial calcium stimulation should be done. Selective arterial calcium stimulation positive for inappropriately elevated insulin secretion is consistent with the diagnosis of NIPHS [3].

We report the case of a 21-year-old female individual with 1p36 deletion syndrome who was found to have NIPHS after hospital admission for persistent falls.

Case Presentation

A 21-year-old female patient with intellectual disability (nonverbal and blind at baseline), congestive heart failure, and epilepsy, secondary to 1p36 deletion syndrome history, was admitted for several months of persistent falls that were progressively worsening. She had no past surgical history. She was diagnosed with 1p36 deletion syndrome (2.6 Mb terminal loss on chromosome 1p36.33p36.32) at age 14. On admission, vital signs were within normal limits and without change in weight, physical examination revealed a thin, nonverbal patient. During hospitalization and prolonged fasting periods

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(14-18 hours) related to poor appetite she developed several episodes of hypoglycemia with serum glucose as low as 57 mg/dL (3.2 mmol/L [70-100 mg/dL; 3.9-5.6 mmol/L]). As the patient was nonverbal with intellectual disability at baseline, subjective symptoms of hypoglycemia such as diaphoresis, lightheadedness, or shakiness were not confirmed. On examination, the patient was observed to have mild akathisia during hypoglycemic episodes. Even when she started to eat, hypoglycemic events continued to occur, mostly while fasting. Dextrose-containing fluids (dextrose 5% and later dextrose 10%) were added to try to maintain blood sugars within the normal range. Despite this therapy, she continued to develop hypoglycemia.

Diagnostic Assessment

Endocrinology service was consulted and recommended obtaining a critical sample. Results of the critical sample (Table 1) revealed a serum glucose of 59 mg/dL (3.3 mmol/L [70-100 mg/dL; 3.9-5.6 mmol/L]), insulin level of 20.6 μIU/mL [123.6 pmol/L [5-15 μIU/mL; 30.0-90 pmol/L]), proinsulin of 33 pmol/L (3.6-22 pmol/L), C-peptide 1.74 ng/mL (0.58 nmol/L [0.8-3.85 ng/mL, 0.27-1.28 nmol/L]), and beta-hydroxybutyrate of < 1.04 mg/dL (< 0.10 mmol/L [< 4.2 mg/dL; < 0.4 mmol/L]). Insulin antibodies were negative. Adrenal insufficiency was unlikely due to a normal morning cortisol level of 13.7 μg/dL (377.98 nmol/L [10-20 μg/dL; 275.9-551.8 nmol/L]). Assessment of insulin-like growth factor 2 (IGF-2) level was not performed as laboratory values were consistent with insulin-mediated hypoglycemia, with elevated insulin, proinsulin, and C-peptide level. Due to the presence of hyperinsulinemia hypoglycemia, further workup was conducted. A computed tomography (CT) of the abdomen with a pancreatic protocol (Fig. 1) and a Ga-68 DOTATATE positron emission tomography (PET)/CT scan were negative for a distinct pancreatic mass. This was followed by an endoscopic ultrasound, which also did not reveal a clear pancreatic mass. At this point in time, further invasive diagnostic evaluation was warranted to identify the source of hyperinsulinism. A selective arterial calcium stimulation test was performed, revealing a two-fold increase in insulin levels in all 3 catheterized pancreatic territories (Table 2).

Treatment

Endocrine surgery was consulted. In the absence of a discrete mass, nonsurgical management was recommended. Medical treatment is traditionally both dietary and pharmacologic. Low glycemic index diet is recommended to prevent strong insulin responses. Diazoxide (ATP sensitive potassium channel agonist), α-glucosidase inhibitors, calcium channel antagonists, or somatostatin analogs are first-line pharmacologic therapy [5]. Nutritional modification was a challenging option for this patient. Diazoxide was considered but due to the patient's history of heart failure, this medication was not started. The decision was to start octreotide injections, 100 mg every 8 hours while she was inpatient, which resulted in resolution of hypoglycemia within hours after the first dose, and complete resolution of hypoglycemic events. Dextrose-containing fluids were stopped after euglycemia was achieved with octreotide. Prior to discharge, the patient was switched to lanreotide 120 mg monthly injections.

Table 1. Critical sample obtained during hospitalization

Serum evaluations	Values	Reference values
Glucose	59 mg/dL [3.3 mmol/L]	70-100 mg/dL [3.9-5.6 mmol/L]
Insulin level	20.6 mIU/mL [123.6 pmol/L]	5-15 mIU/mL [30.0-90.0 pmol/L]
C-peptide	1.74 ng/mL [0.58 nmol/L]	0.8-3.85 ng/mL [0.27-1.28 nmol/L]
Proinsulin	33 pmol/L	3.6-22 pmol/L
Insulin antibodies	negative	negative
Beta-hydroxybutyrate	< 1.04 mg/dL [< 0.10 mmol/L]	< 4.2 mg/dL [< 0.4 mmol/L]
Cortisol	13.7 mg/dL [377.98 nmol/L]	10-20 mg/dL [275.9-551.8 nmol/L]

Conversion factors used for conversion of conventional units to SI units are below: Glucose: 1 mg/dL = 0.06 mmol/L; Insulin: 1 μIU/mL = 6.0 pmol/L; C-peptide: 1 ng/mL = 0.33 nmol/L; Proinsulin: conventional units are SI units; no conversion; Insulin antibodies: conventional units are SI units; no conversion; Beta-hydroxybutyrate: 1 mg/dL = 10.42 mmol/L; Cortisol: 1 mg/dL = 27.59 nmol/L.

Outcome and Follow-Up

The patient was discharged to an assisted living facility. She continued receiving monthly lanreotide injections and following up with endocrinology outpatient service. She did well on monthly injections for over a year with no hypoglycemic episodes nor falls. Due to difficulties with insurance, she was later transitioned to diazoxide 20 mg 3 times a day. She has had no further admissions related to hypoglycemia and her glucose has remained in the 80 to 100 mg/dL range (4.4-5.6 mmol/L).

Discussion

To our knowledge, this is the first case reported of NIPHS in a patient with 1p36 deletion syndrome. Chromosomal 1p36 deletion has been occasionally reported to have an association with Prader-Willi-like phenotype [6]. One case report describes 2 pediatric patients with 1p36 deletion who were found to have hyperinsulinism in the setting of type 2 diabetes mellitus (hemoglobin A1C of 6.1%-6.6%), obesity (BMI 26-27 kg/m^2), and hyperphagia [6]. The patients in this report were diagnosed with Prader-Willi-like phenotype when they were children (6 and 10 years old, respectively). At the time of diagnosis, they already had obesity, diabetes, and insulin resistance with insulin levels of 49-54 μIU/mL (294-324.0 pmol/L). However, our adult patient who was diagnosed with 1p36 deletion syndrome at age 14 lacked the Prader-Willi-like phenotype described, with a BMI of 20.9 kg/m^2 and had decreased appetite. Additionally, this patient's workup did not reveal any findings of insulin resistance and her hemoglobin A1C was 5.1%.

Although a significant proportion of known nesidioblastosis patients developed NIPHS following gastric bypass surgery, the etiology of idiopathic nesidioblastosis is not currently known [3]. A variety of distinct causes of idiopathic NIPHS may exist and are rare, with less than 600 reported cases [5, 7]. NIPHS typically presents with postprandial hypoglycemia but fasting hypoglycemia has also been reported. Fasting hypoglycemia does not exclude NIPHS, nor does postprandial hypoglycemia rule out an insulinoma [5].

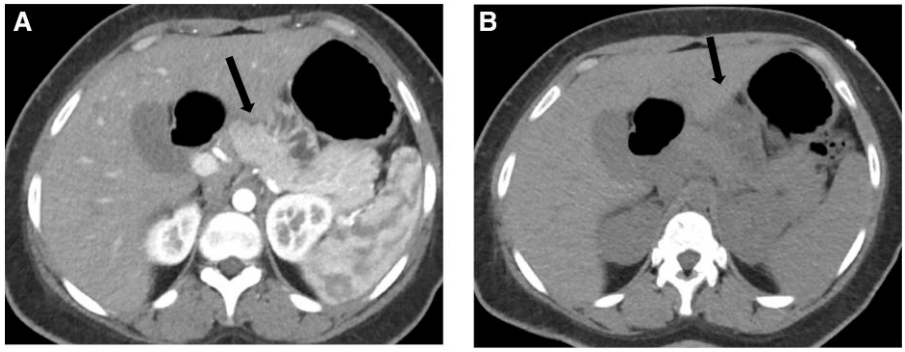

Figure 1. CT pancreatic protocol with (A) and without contrast (B). Black arrow is pointing out the pancreas.

Table 2. Selective arterial calcium stimulation test results

Time elapsed (seconds)	Insulin-stimulated celiac artery	Insulin-stimulated superior mesenteric artery	Insulin-stimulated dorsal pancreatic artery	Insulin-stimulated splenic artery
Baseline	4.7 µIU/mL [28.2 pmol/L]	5.0 µIU/mL [30.0 pmol/L]	30.6 µIU/mL [183.6 pmol/L]	21.1 µIU/mL [126.6 pmol/L]
0	7.1 µIU/mL [42.6 pmol/L]	15.3 µIU/mL [91.8 pmol/L]	50.1 µIU/mL [300.6 pmol/L]	24.6 µIU/mL [147.6 pmol/L]
30	12.2 µIU/mL [73.2 pmol/L]	34.0 µIU/mL [204.0 pmol/L]	125.0 µIU/mL [750 pmol/L]	40.8 µIU/mL [244.8 pmol/L]
60	16.1 µIU/mL [96.6 pmol/L]	31.4 µIU/mL [188.4 pmol/L]	89.9 µIU/mL [539.4 pmol/L]	34.1 µIU/mL [204.6 pmol/L]

Values measured using intraarterial monitoring.

NIPHS has previously been reported as comorbid with insulinoma [7], heterotopic pancreas (with nesidioblastosis histology seen in pancreas and heterotopic pancreas tissue) [8], and concomitant pancreatic neuroendocrine tumor and intraductal papillary mucinous neoplasia [9]. Each of these cases were successfully treated with surgery. The concomitant pancreas pathology in these cases is rare and have very rarely been reported in association with NIPHS.

In the patient reported here, it is unclear if NIPHS and 1p36 deletion syndrome share any pathologic mechanisms. One possibility for this link could be that the absent genetic material in this syndrome may also play a role in the pancreatic β-cells. Some literature theorizes a genetic cause, as the majority of idiopathic cases are diagnosed in children (genes such as *ABCC8*, *KCNJ11*) [10] but further studies are needed to fully elucidate this mechanism in adults [4]. Two genes known to cause NIPHS in children via ATP sensitive potassium channel responsible for glucose induced insulin secretion by the pancreatic-cell, SUR1 and Kir6.2, have not been found to cause NIPHS in adult diagnoses [11].

Learning Points

- 1p36 deletion syndrome and nesidioblastosis are both rare conditions and have not previously been reported to be interrelated.
- Nesidioblastosis requires careful work up including serologic testing, imaging studies, and selective arterial calcium stimulation testing.
- Hypoglycemic events may be underdiagnosed in nonverbal patients with underlying cognitive disability.

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Contributors

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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