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HYPERINSULINISM PRESENTING IN CHILDHOOD AND TREATMENT BY CONSERVATIVE PANCREATECTOMY

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Abstract

Objective—To describe the uncommon presentation of hyperinsulinism in an 8-year-old boy.

Methods—We describe the patient's clinical findings, results from biochemical and imaging studies, surgical approach, and outcome. The discussion encompasses a review of literature that provided the basis for the diagnostic and surgical approach applied to this patient's case.

Results—An obese 8.5-year-old boy initially presented with hypoglycemic seizures after initiation of dietary changes to treat obesity. Biochemical analysis indicated hyperinsulinism. Endoscopic ultrasonography showed no pancreatic lesions suggestive of insulinoma. Genetic studies identified no known mutations in the *ABCC8*, *KCNJ11*, *GCK*, or *GLUD1* genes. Selective arterial calcium stimulation and hepatic venous sampling did not document a focal source for hyperinsulinism in the pancreas, and positron emission tomography with 18-fluoro-L-3,4-dihydroxyphenylalanine showed diffusely increased uptake in the pancreas. The patient ultimately required partial pancreatectomy because of continued hypoglycemia while taking diazoxide and octreotide. Intraoperative glucose monitoring directed the extent of surgical resection. A 45% pancreatectomy was performed, which resolved the hypoglycemia but led to impaired glucose tolerance after surgery.

Conclusion—The unusual presentation of hyperinsulinism in childhood required a personalized approach to diagnosis and surgical management using intraoperative glucose monitoring that resulted in a conservative pancreatectomy.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

INTRODUCTION

Persistent hyperinsulinemic hypoglycemia usually presents in the newborn period, and it can result from focal or diffuse pancreatic β -cell hypersecretion. Genetic mutations in *ABCC8* (formerly *SURI*), *KCNJ11* (Kir6.2), *GCK* (glucokinase), and *GLUD1* (glutamate dehydrogenase) are found in only 50% of cases with hyperinsulinism. Infants requiring surgery for diffuse hyperinsulinism usually undergo near-total (95%-98%) pancreatectomy (1). However, some patients have residual hypoglycemia or develop diabetes mellitus. Childhood insulinoma, while uncommon, has been described in the literature (2,3). Minimal information is available on the etiology and management of hyperinsulinism in childhood. This report describes a rare case of hyperinsulinism presenting in childhood, the biochemical and radiologic evaluation conducted in the attempt to differentiate between focal and diffuse disease, and the personalized surgical management by conservative pancreatectomy.

CASE REPORT

The patient was an obese 8.5-year-old white/Mexican boy who initially presented with seizures after initiation of dietary changes for obesity. The paramedics were called, and his blood glucose concentration measured upon the paramedics' arrival was 30 mg/dL. Low blood glucose levels persisted despite dextrose administration in the emergency department. The patient's medical history was notable for only obesity. The parents were nonconsanguineous. There was no family history of hypoglycemia, diabetes, or neuroendocrine disease. His father had epilepsy. Physical examination findings were normal. The patient was prescribed diazoxide, 5 mg/kg daily (typical dosage range for newborns and infants is 8-15 mg/kg daily; for children and adults 3-8 mg/kg daily); instructed on home glucose monitoring; and discharged home.

The patient was hospitalized 2 months later because of formal laboratory test results that were obtained while the patient was fasting and not taking diazoxide. Laboratory tests performed during fasting hypoglycemia revealed the following results (reference ranges in parentheses): glucose, 40 mg/dL (70-105 mg/dL); cortisol, 12 μ g/dL (6.2-19.4 μ g/dL); normal fatty acid profile; glucagon, 79 pg/mL (40-130 pg/mL); insulinlike growth factor-binding protein 1, 3.2 ng/mL (30-1000 ng/mL); C-peptide, 1.1 ng/mL (0.9-4.3 ng/mL); growth hormone, 0.4 ng/mL (<1.5 ng/mL); and insulin, 52 μ IU/mL (2.0-17.8 μ IU/mL). His body mass index (BMI) was 33 kg/m² (weight 65.7 kg). Abdominal computed tomography imaging was normal. The patient was discharged home on diazoxide, 4.5 mg/kg daily.

At 10 years of age, the patient was evaluated further after transferring care to our medical center. His BMI was 44 kg/m² (weight 103.5 kg), and he had acanthosis nigricans. Before taking morning medications, the following laboratory results were documented (reference ranges in parentheses): serum glucose, 55 mg/dL (70-99 mg/dL); proinsulin, 5.9 ng/mL (<0.20 ng/mL); C-peptide, 3.8 ng/mL (0.8-4.0 ng/mL); and insulin, 9.9 μ IU/mL (1.9-23.0 μ IU/mL). When he was formally fasting, his serum glucose concentration was 38 mg/dL (70-99 mg/dL) at 18.5 hours, with an insulin concentration of 8 μ IU/mL (1.9-23.0 μ IU/mL) and a C-peptide concentration of 4.2 ng/mL (0.8-4.0 ng/mL). After simultaneous infusions of insulin (0.05 units/kg per hour) and dextrose for 180 minutes, the patient's C-peptide level failed to suppress (2.0 ng/mL [0.8-4.0 ng/mL]) when his glucose concentration was 37 mg/dL (65-160 mg/dL). The patient did not have urinary ketones or elevated ammonia levels during hypoglycemia, and he exhibited glucagon responsiveness. A serum hypoglycemia screen for common diabetes medications was negative. Genetic testing did not identify mutations in the *ABCC8*, *KCNJ11*, *GLUD1*, or *GCK* genes (Athena Diagnostics). Endoscopic ultrasonography of the pancreas showed no lesions suggestive of insulinoma. Chromogranin A level was normal.

The patient underwent selective arterial calcium stimulation and hepatic venous sampling (4), and his insulin levels did not demonstrate a regional response to the calcium injections. While the patient was not taking diazoxide, positron emission tomography was performed with 5.3 mCi (196 MBq) of 18-fluoro-L-3,4-dihydroxyphenylalanine (¹⁸F-DOPA). The human subjects committee at the Los Angeles Biomedical Research Institute at Harbor-UCLA approved compassionate use of ¹⁸F-DOPA. The patient and his guardian signed written informed consent. The images demonstrated diffuse uptake throughout the pancreas and no focal lesion was identified (Fig. 1).

Medical management was attempted. The patient's condition initially responded to diazoxide (4.5 mg/kg daily). He attempted to lose weight by eating small, frequent meals, and he reached a BMI of 30 kg/m² (weight 78.7 kg). When the patient's hypoglycemia eventually worsened, diazoxide dosage escalation up to 8 mg/kg daily was attempted, but the patient progressively gained weight (highest BMI 48.5 kg/m², weight 139.3 kg) and outgrew his dosage. His last dosage was 4 mg/kg daily (525 mg daily). Addition of octreotide, 50 mcg twice daily by sub-cutaneous injection, did not eliminate hypoglycemic episodes, although the events occurred in the 40- to 50-mg/dL range instead of the 20- to 40-mg/dL range. The patient was in a personalized education program at school because hypoglycemic episodes regularly interfered with his learning, but he did not have neurocognitive defects.

Because medical therapy failed, the patient underwent a 45% distal pancreatectomy with splenectomy at age 15 years. Preoperative glucose concentrations were as low as 48 mg/dL (65-110 mg/dL). No focal lesions were identified intraoperatively by palpation or ultrasonography. Intraoperative glucose levels were used to guide extent of pancreatectomy (Fig. 2). Ten minutes after an initial 25% resection of the pancreas, the dextrose infusion was stopped temporarily, and the patient's intraoperative glucose concentration rose to 115 mg/dL. To account for dextrose already received and intraoperative stress, a final 20% resection was performed, and the glucose concentration rose to 143 mg/dL. Four hours after surgery, the blood glucose was 221 mg/dL on 5% dextrose intravenous fluids. Laboratory test results from the morning after surgery (off dextrose) were as follows: glucose, 154 mg/dL (65-110 mg/dL); C-peptide, 7.4 ng/mL (0.8-3.1 ng/mL); insulin 41, μ IU/mL (5-27 μ IU/mL); and proinsulin, 66.5 pmol/L (2.1-26.8 pmol/L).

Gross and microscopic examination of serial histologic sections along the 9-cm resected pancreatic body and tail revealed normal architecture. The parenchyma consisted of typical pancreatic lobules with the exocrine tissue divided normally into acini. The islets were scattered among the exocrine pancreas in the usual way. No coalescent islet focality, islet neoplasia, or adenomatous foci was present. The only abnormality was conspicuous islet anisonucleosis in the form of enlarged islet cell nuclei seen throughout the pancreatic islets. The enlarged nuclei were greater than 3 times the diameter of the surrounding more typical islet cell nuclei (Fig. 3).

Postoperatively, the patient no longer required diazoxide or octreotide. At home, his blood glucose concentration ranged from 88 to 262 mg/dL. Six months after surgery, the patient had an impaired fasting glucose concentration of 107 mg/dL (70-99 mg/dL) with an insulin concentration of 9.2 μ IU/mL (1.9-23.0 μ IU/mL) (homeostasis model assessment of insulin resistance, 2.43; BMI, 46.6 kg/m²; weight, 131.4 kg). His 2-hour serum glucose concentration after ingestion of 75 g of glucose was 196 mg/dL (65-160 mg/dL) with an insulin level of 52.5 μ IU/mL (1.9-23.0 μ IU/mL), thus indicating impaired glucose tolerance. The patient continued to receive nutritional counseling with advice to lose weight to prevent overt diabetes. One year after surgery, his BMI was 42 kg/m² (weight 123.3 kg), and his fasting blood glucose concentration was 78 mg/dL. His 2-hour blood glucose concentration after 75-g glucose ingestion was 190 mg/dL, with a hemoglobin A_{1c} level of 5.0%.

DISCUSSION

This rare case illustrates the challenges in diagnosis and management of hyperinsulinism from pancreatic islet cell hypersecretion in childhood. The approach to diagnosis encompassed techniques used in evaluation of insulinoma and focal or diffuse hyperinsulinism. After confirming inappropriate hyperinsulinemia during fasting and C-peptide suppression, insulinoma was higher on the differential diagnosis because of his age. Once endoscopic ultrasonography showed no suspicious lesions, diffuse or focal hyperinsulinism became the leading diagnosis. We considered the possibility that overnutrition had masked hypoglycemia from congenital hyperinsulinism, leading to obesity. However, adult-onset cases of hyperinsulinism have been reported (5), so childhood-onset disease in this patient is probable. Examination of the literature yielded very little information on management of focal or diffuse hyperinsulinism in this patient's age group.

Distinguishing between diffuse and focal hyperinsulinism is important because the diagnosis may direct surgical management. Selective arterial calcium stimulation and hepatic venous sampling did not localize an affected area of the pancreas in this patient. Positron emission tomography with ^{18}F -DOPA has been reported to accurately discriminate focal from diffuse hyperinsulinism in neonates (6), although this method may have limited value in adults with insulinoma (7). The ^{18}F -DOPA positron emission tomography scan in this patient was suggestive of diffuse disease.

Long-term medical therapy is an option for treatment of diffuse hyperinsulinism (8). The patient was treated as if he had diffuse disease, but medical management failed and surgery was indicated. Reports have shown that many infants with congenital diffuse hyperinsulinism undergo near-total pancreatectomy (9). In rare cases of adult-onset diffuse hyperinsulinism, 70% pancreatectomy has been performed with cure or some persistent disease (5). However, no information in the literature is available to guide extent of pancreatectomy in a patient such as this. This patient's insulin resistance from obesity further complicated estimation of the extent of pancreatectomy needed. However, research in animals has shown that 50% reduction of β -cell mass induces impaired fasting glucose and glucose intolerance (10). Measurement of intraoperative glucose levels was the surgical team's clinical approach that served as the primary guide to direct extent of resection. Forty-five percent resection may have been just enough in the setting of insulin resistance, but the future will tell if this was optimal for this patient.

The key histopathologic diagnostic criterion for diffuse hyperinsulinism (11-13) is islet cell nuclear enlargement scattered throughout the pancreatic islets and no focal aggregation of islet tissue (14). Three-fold nuclear enlargement of some islet cell nuclei as compared with adjacent normally sized nuclei (anisonucleosis), as demonstrated in this patient, is the visual cue to diagnosis. Although there was no specimen from the pancreatic head to complete the evaluation, the patient did not demonstrate acinar tissue impingement or lobule distortion from nodular growth of islet tissue that occurs in focal adenomatosis, outside of which normally sized nuclei would be seen (13). Our leading diagnosis is therefore diffuse hyperinsulinism. However, atypical cases of focal nuclear enlargement have been described (15,16). The possibility that this patient's pathologic findings could be attributable to obesity and insulin resistance was considered, as islet cell hyperplasia in obesity and insulin resistance has been described (17-19), but a lack of data in humans supporting associated nuclear enlargement makes this possibility speculative.

CONCLUSION

This patient presented with hyperinsulinism during childhood. A conservative pancreatectomy resulted in resolution of hypoglycemia, although he remained glucose intolerant. An approach to surgical management using intraoperative glucose measurements should be considered as a possible method of optimizing outcome in patients with hyperinsulinism.

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Abbreviation

BMI body mass index

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Fig. 1.

Anterior view of 18-fluoro-L-3,4-dihydroxyphenylalanine positron emission tomography 3-dimensional reconstruction showing increased uptake throughout the pancreas.

Fig. 2.

Intraoperative and postoperative glucose concentrations by point-of-care testing. The lowest glucose concentration before pancreatic resection was 48 mg/dL. After initial 25% pancreatic resection, the glucose concentration rose to 115 mg/dL. After 20% further resection, the glucose concentration rose to 143 mg/dL.

Fig. 3.

Islets from the patient, demonstrating conspicuous anisonucleosis in both the tail (*Panel A*) and the body (*Panel B*) of the pancreas (hematoxylin and eosin stain, $\times 600$ magnification). The enlarged nuclei were found in islets throughout the resected pancreatic tissue.