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Hyperinsulinemic Hypoglycemia Due to an Insulinoma in a 2-Year-Old Child

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Abstract

Insulinomas are rare insulin-secreting tumors that most commonly affect adults. A 26-month-old child presented to her local emergency department with severe hypoglycemia. Initial workup was consistent with hyperinsulinemic hypoglycemia. Over the course of 10 months, multiple therapies for hyperinsulinism (HI) were trialed without significant benefit. Genetic testing for genes associated with HI was negative. At age 35 months, the patient was transferred to our center for further treatment. She underwent several imaging tests that revealed a lesion on her pancreas concerning for an insulinoma. The patient underwent surgical intervention to enucleate the lesion. Histopathological review of the specimen confirmed a benign, well-circumscribed insulinoma. A postoperative fasting test proved the patient was cured and she was discharged without the need for further glucose monitoring.

Key Words: insulinoma, hyperinsulinism, pancreas, hypoglycemia, case report, pediatric

Abbreviations: ^{18}F-DOPA, ^{18}F-fluoro-dihydroxyphenylalanine; HI, hyperinsulinism; IV GIR, intravenous glucose infusion rate; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

Introduction

Hyperinsulinemic hypoglycemia is the most common cause of persistent hypoglycemia in children and adults (1). In young children, this is most commonly due to congenital hyperinsulinism (HI) resulting from defects in genes that regulate insulin secretion (2). In adolescents and adults, insulin-secreting neuroendocrine tumors, insulinomas, most frequently cause hyperinsulinemic hypoglycemia (3). In both conditions, excessive insulin secretion results in persistent hypoketotic hypoglycemia (1).

Insulinomas are rare, affecting 1 to 4 of 1 000 000 people, and are benign in 90% of cases (4). The average age of presentation for insulinomas has been reported as 47 years with very few reports of pediatric-acquired insulinomas existing in the literature (5, 6). Our team previously described a cohort of 8 pediatric and young adult patients with insulinoma seen over the course of 13 years at our institution (6). Padidela et al (2014) (7) echoed our findings as they wrote of their experience at 2 referral centers for pediatric hyperinsulinemic hypoglycemia in the United Kingdom over the course of

12 years and found only 9 insulinoma cases. More recently, Melikyan et al (2023) (8) described a cohort of 22 pediatric insulinoma cases seen over 26 years at their referral center in Russia.

Insulinomas are typically small tumors; a study of 50 patients treated for insulinomas found only 4% of lesions were greater than 3 cm (9). Given their small size, localization of the tumor can be difficult and multiple imaging modalities may be required (10). Surgical resection is often curative but requires preoperative localization to avoid high-risk pancreatic exploration. Together, this emphasizes the importance of 1) timely and accurate diagnosis and 2) comprehensive imaging to localize the insulinoma for surgical resection to prevent the adverse neurological sequalae from prolonged periods of hypoglycemia (11).

In patients presenting with acute-onset hypoglycemia, it is important to thoroughly investigate the root cause of hypoglycemia by obtaining a "critical blood sample" during a spontaneous or provoked episode of hypoglycemia to measure metabolic fuels and hormone levels (12). Pediatric patients presenting with hyperinsulinemic hypoglycemia outside

Table 1. Critical sample data and interpretation ([14])

	Initial presentation to local hospital	On admission at our hospital	Prior to discharge from our hospital
Duration before hypoglycemia, h	0 (spontaneous hypoglycemia)	4	19
Plasma glucose[a]	26 mg/dL (1.4 mmol/L)	64 mg/dL (3.6 mmol/L)	46 mg/dL (2.6 mmol/L)
Urine ketones[b]	Trace	Not obtained	Not obtained
Insulin[c]	3.4 µIU/mL (23.63 pmol/L)	Not obtained	<2.0 µIU/mL (<13.9 pmol/L)
β-Hydroxybutyrate[d]	Not obtained	3.1 mg/dL (<0.3 mmol/L)	20.8 mg/dL (2.0 mmol/L)
Free fatty acid[e]	Not obtained	Not obtained	77.18 mg/dL (2.74 mmol/L)
C-peptide[f]	1.01 ng/mL (0.33 nmol/L)	Not obtained	0.2 ng/mL (0.07 nmol/L)
IGFBP-1[g]	Not obtained	Not obtained	96 ng/mL (12.6 nmol/L)
Glucagon stimulation result[b]	Not obtained	Not obtained	Negative

Abbreviation: IGFBP-1, insulin-like growth factor binding protein 1.

[a]Normal reference range 74 to 127 mg/dL (4.1-7.1 mmol/L).

[b]Should be elevated (moderate or high) during hypoglycemia.

[c]Should be undetectable during hypoglycemia.

[d]Should be more than 18.7 mg/dL (>1.8 mmol/L) during hypoglycemia.

[e]Should be more than 42.3 mg/dL (>1.5 mmol/L) during hypoglycemia.

[f]Should be less than 0.5 ng/mL (<0.17 nmol/L) during hypoglycemia.

[g]Should be 10 to 500 ng/mL (1.3-65.5 nmol/L) from a random draw.

[h]Should be negative (indicating a Δ increase of plasma glucose less than 30 mg/dL [1.7 mmol/L]).

infancy present a particular diagnostic challenge in that the clinician must distinguish between insulinoma and congenital hyperinsulinism. When indicated, imaging to rule out a surgically resectable lesion, such as focal HI or an insulinoma, should be obtained ([13]).

We report the case of a 2-year-old child with hyperinsulinemic hypoglycemia with suspected congenital hyperinsulinism who, on imaging, was found to have a small pancreatic insulinoma.

Case Presentation

The patient was born full-term at 38 weeks' gestation following an uncomplicated pregnancy. Her birth weight was appropriate for gestational age and she had a postnatal complication of jaundice not requiring phototherapy. She continued in good health and developed appropriately (developmental milestones met as expected; height 50th percentile and weight 41st percentile) until approximately age 25 months, when her parents reported increased sleepiness and episodes of shaking on awakening. At 26 months, she was found seizing in the early morning. A plasma glucose obtained by emergency services was 14 mg/dL (0.8 mmol/L; normal reference range, 74-127 mg/dL; 4.1-7.1 mmol/L). There was no reported family history of hypoglycemia.

Diagnostic Assessment

On arrival at the local hospital, her physical examination was unremarkable. A critical sample was consistent with hyperinsulinemic hypoglycemia: plasma glucose 26 mg/dL (1.4 mmol/L), insulin 3.4 µIU/mL (should be undetectable during hypoglycemia), and C-peptide of 1.01 ng/mL (should be

<0.5 ng/mL during hypoglycemia; [Table 1]). Growth hormone and cortisol levels during this admission were reportedly normal. She was initiated on diazoxide 15 mg/kg/day. Her oral food intake decreased over the subsequent month, and she re-presented to the local emergency department twice for severe hypoglycemia. A percutaneous endoscopic gastrostomy tube was placed both for nutrition feedings and rescue dextrose boluses. Genetic testing for congenital hyperinsulinism (analyzed by Athena Diagnostics) and glycogen storage diseases (analyzed by Duke University Health System) were negative.

Throughout the subsequent 10 months, episodes of severe hypoglycemia continued. She was trialed on octreotide (15.4 mcg/kg/day), nifedipine (1 mg/kg/day), and uncooked cornstarch (2 tablespoons every 4 hours) concomitantly with maximum-dose diazoxide and continuous gastrostomy tube feedings. Unfortunately, these multiple therapies did not effectively prevent hypoglycemia.

At the time of transfer to our hospital, the patient was being treated with supratherapeutic doses of diazoxide (16.8 mg/kg/day) and an intravenous glucose infusion rate (IV GIR) of 3.5 mg/kg/min. This indicates that diazoxide therapy alone was insufficient to prevent hypoglycemia and an IV infusion of concentrated dextrose in normal saline (in this case, providing 3.5 mg/kg/min of glucose) was required to maintain euglycemia. She was also receiving continuous feeds via gastrostomy tube.

On admission to Children's Hospital of Philadelphia, physical examination was unremarkable except for hypertrichosis consistent with diazoxide therapy. A fasting test revealed she was unable to maintain plasma glucose greater than 70 mg/dL (3.9 mmol/L) for more than 4 hours while on diazoxide. Given this result, diazoxide was discontinued and her IV GIR was
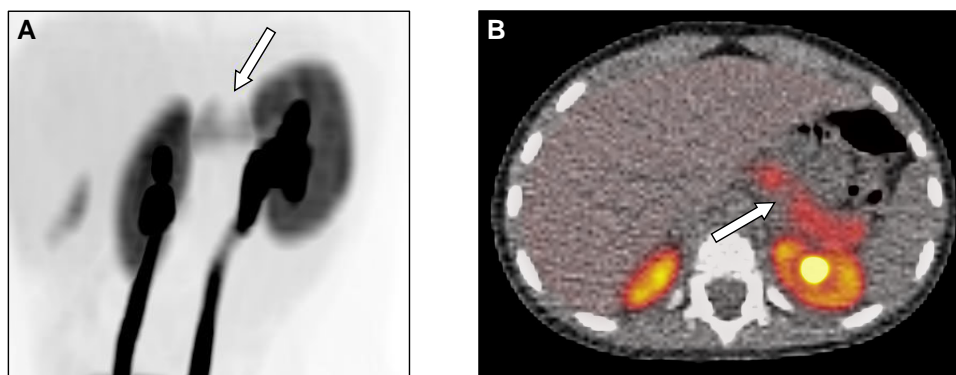
Figure 1. Positron emission tomography/computed tomography imaging. A, ^{18}F-DOPA PET/CT, 3D-maximum intensity projection shows homogenous uptake of radiotracer in the normal pancreatic tissue surrounding a round focus of photopenia (arrow). There are no foci of increased uptake. B, Axial PET/CT fused image also confirms the photopenic area (arrow) in the pancreatic body.
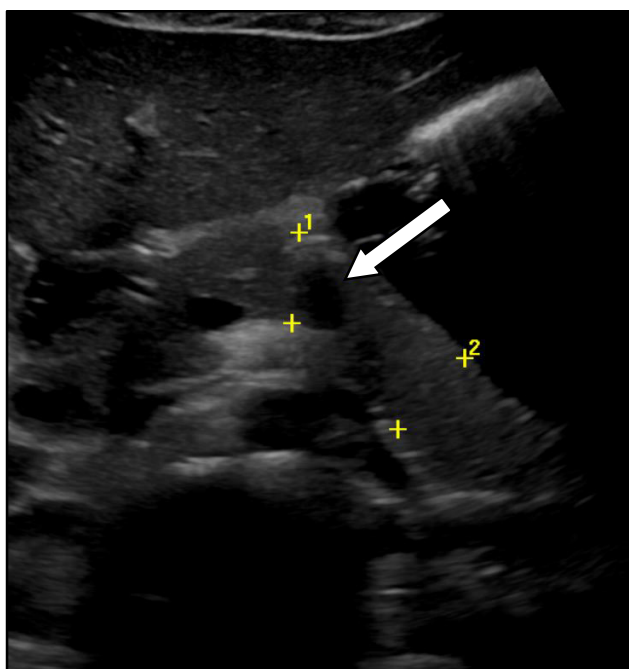
Figure 2. Abdominal ultrasound imaging. Abdominal ultrasound shows a round, hypoechoic, solid lesion in the pancreatic body (arrow) corresponding to the site of focal photopenia on the ^{18}F-DOPA PET/CT.

titrated to maintain euglycemia while feedings were condensed from continuous to boluses every 6 hours.

A chromosomal single-nucleotide variation microarray (analyzed by Children's Hospital of Philadelphia) and additional genetic testing for HI (analyzed by University of Pennsylvania), including testing for Kabuki syndrome (analyzed by Children's Hospital of Philadelphia), were obtained, all of which were negative. The patient was not tested for Beckwith-Wiedemann syndrome given her lack of clinical features and her age at presentation of hypoglycemia. She underwent imaging with ^{18}F-fluoro-dihydroxyphenylalanine (^{18}F-DOPA) positron emission tomography/computed tomography (PET/CT) scan to determine if her HI was focal. In focal hyperinsulinism, there is increased ^{18}F-DOPA uptake by the large-type amino acid transporter systems found in the β cells comprising the focal lesion compared to surrounding normal tissue (15, 16). For this child, however, the ^{18}F-DOPA PET/CT imaging showed homogenous radiotracer uptake in the pancreas with a photopenic defect in the pancreatic body compared to normal pancreas tissue (Fig. 1). As such, these findings were not consistent with focal hyperinsulinism.

Ultrasound imaging redemonstrated a hypoechoic ovoid focus in the mid pancreatic body, corresponding to the lesion identified by ^{18}F-DOPA PET/CT, that was not consistent with a cyst due to the lack of posterior acoustic enhancement nor a focal parenchymal lesion (Fig. 2). Magnetic resonance imaging (MRI) revealed a T1-hypointense $1.4 \times 1.2 \times 1.1$ cm solid lesion in the pancreatic body with a rim of contrast enhancement corresponding to the photopenic defect on the ^{18}F-DOPA PET/CT (Fig. 3), a pattern characteristic of an insulinoma (4). At this time, additional genetic testing specific for mutations in *MEN1* (analyzed by Prevention Genetics) was sent, which was negative.

Treatment

Throughout the admission, plasma glucose was managed with dextrose-containing fluids at rates ranging from 1.7 to 6.2 mg/kg/min. On localization of the lesion, a surgical laparotomy was performed that identified a lesion on the anterior superior surface of the pancreatic body. Grossly, the lesion was described as an approximately 1-cm round, encapsulated, bluish-colored mass. The lesion was successfully enucleated during the procedure. A distal 40% pancreatectomy was then completed given potential pancreatic duct damage. Histopathological review of the lesion confirmed a well-circumscribed, encapsulated neuroendocrine tumor comprised entirely of β cells and void of exocrine tissue and ducts, consistent with an insulinoma (Fig. 4) and exclusionary for a focal lesion.

Specifically, in insulinomas, the neoplastic proliferation is limited to the β-cell population and the corresponding histology is that of a monotonous population of tumor cells that is typically well circumscribed and often encapsulated. Alternatively, the increase in endocrine cells seen in focal lesions results from loss of growth inhibition due to loss of heterozygosity for the maternal 11p15.1 region within affected cells that contain imprinted genes involved in cell proliferation. As such, focal lesions consist of an increased number of endocrine cells (including α, δ, and β cells), but also incorporate variable amounts of acinar tissue and duct structures.
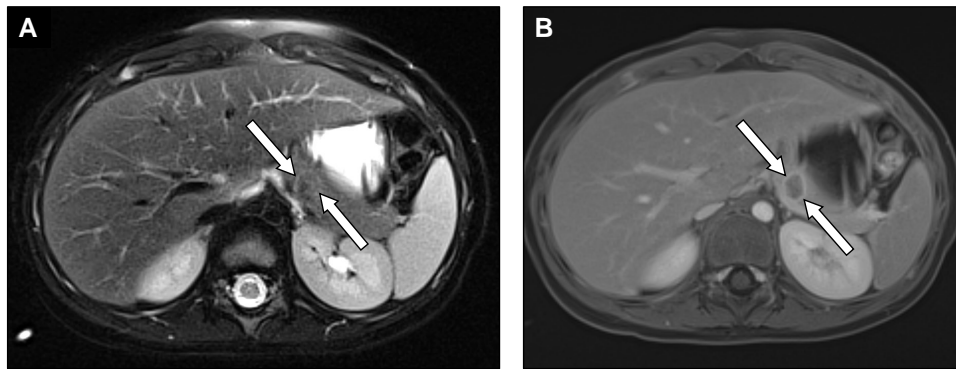
Figure 3. Magnetic resonance imaging. A, Magnetic resonance T2-weighted, fat-saturated image shows a heterogeneous lesion in the pancreatic body measuring 1.4 × 1.2 cm (arrows) with a rim of increased T2 signal. B, T1-weighted fat-saturated, contrast-enhanced image in the portal venous phase shows a hypoenhancing mass with a rim of contrast enhancement (arrows).
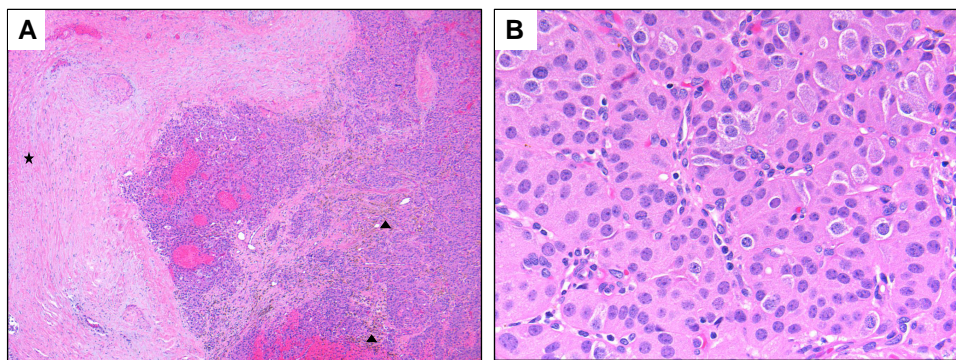
Figure 4. Histopathology of lesion. Hematoxylin and eosin–stained histologic sections of the tumor demonstrated a well-circumscribed proliferation of endocrine cells bounded by a variably dense fibrous capsule (star). A, Areas of hemosiderin deposition were also present (arrowheads) (50× original magnification). B, Cells have abundant eosinophilic cytoplasm with stippled chromatin pattern; no significant mitotic activity was identified (400× original magnification).

The abnormal endocrine tissue of focal lesions is not usually encapsulated and can also extend into adjacent lobules (17). Patchy areas of hemosiderin deposition consistent with prior intralesional hemorrhage and focal necrosis were also present. Overall mitotic activity was low (<2 mitoses/2 mm^2).

Genetic testing from resected tumor tissue (analyzed by Children's Hospital of Philadelphia) revealed a novel variant in *TSC2* (c.648 + 2T > G) with a low variant allele frequency that likely results in the skipping of exon 7 and may have been a somatic cause of the child's insulinoma. Germline variants in *TSC2* have been previously reported in patients with sporadic insulinomas but phenotypic data on clinical presentation remain lacking (18).

Outcome and Follow-up

Postoperatively, the patient had no further hypoglycemia. Prior to discharge, she underwent an 18-hour fast that demonstrated resolution of hyperinsulinemic hypoglycemia (see Table 1). She was discharged without the need for further home glucose monitoring or endocrine follow-up. To date, this is the youngest patient with an insulinoma to be diagnosed and cured at our center.

Discussion

As emphasized by the Endocrine Society and the Pediatric Endocrine Society published guidelines, fasting tests are the gold standard for evaluating children and adults with persistent hypoglycemia (12, 19). However, the biochemical diagnosis of insulinomas may remain undistinguishable from that of congenital hyperinsulinism, which is more common in young children; thus, a high index of suspicion is needed to diagnose insulinomas in young children. As was the case for our patient, the sudden onset of symptoms without a history of neonatal hypoglycemia was consistent with an acquired, rather than a congenital, process.

In patients with suspected insulinomas, imaging is required prior to surgical intervention, which may require multiple modalities including ultrasound, endoscopic ultrasound, MRI, CT, and PET/CT. Localization of insulinomas is challenging given their small size and variable imaging characteristics (20). Had we not localized the insulinoma in this patient through imaging, our practice would have been to optimize medical management and repeat imaging every 6 months.

Pediatric insulinomas are exceedingly rare (6). We present here a case of a 2-year-old female patient in otherwise normal health with acute-onset, severe hypoglycemia. Given her age at presentation, congenital hyperinsulinism was the suspected diagnosis. Through thorough imaging, she was found to have a small insulinoma. The lesion was enucleated intraoperatively and she was cured. This case highlights the importance of thorough diagnostic assessment for pediatric patients presenting with persistent hypoketotic, hyperinsulinemic hypoglycemia outside infancy.

Learning Points

- Similar to adults, pediatric patients with insulinomas present with acute-onset, symptomatic hypoglycemia.
- Presentation of hyperinsulinemic hypoglycemia after infancy warrants an insulinoma workup consisting of multiple imaging modalities.
- Surgery is often curative, and the risk of recurrence is low in genetics-negative cases.

Informed Patient Consent for Publication

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

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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