Sporadic Insulinoma Presenting as Early Morning Night Terrors

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A 16-year-old boy with a recent diagnosis of night terrors was evaluated for recurrent early morning hypoglycemia after an early morning seizure. Evaluation in clinic with critical laboratories identified hyperinsulinemic hypoglycemia. Additional investigation revealed a sporadic insulinoma as the etiology of his hypoglycemia and all symptoms were resolved after pancreaticoduodenectomy. The importance of obtaining critical laboratory samples is highlighted and appropriate radiologic, medical, and pathologic testing is discussed. We additionally review the medical and surgical management of hyperinsulinemic hypoglycemia. A discussion of multiple endocrine neoplasia type 1 associated insulinomas is included as well. This case highlights the importance of considering hypoglycemia in the evaluation of night terrors and new-onset seizures.

Insulinoma is a rare (1:500 000) neuroendocrine tumor presenting with hyperinsulinemic hypoglycemia.[1,2] The rarity of this condition in children[3] and its varied presentation makes this a challenging diagnosis. In this report, we describe the case of a patient previously diagnosed with night terrors based on 3 episodes of early morning altered mentation. The patient subsequently experienced an early morning seizure that brought him to the emergency department (ED), where he was found to be hypoglycemic and later diagnosed with an insulinoma. This case highlights the importance of maintaining a high suspicion of hypoglycemia in patients who develop altered mentation after prolonged fasting, such as in the early morning hours after a night of sleep.

CASE REPORT

J.S. is a 16-year-old boy with no past medical history. Beginning 8 months before presentation, he experienced 3 sporadic episodes in which he awoke in the early morning screaming/yelling, observed by his mother, and which self-resolved after 5 to 10 minutes. He was unable to recall these events and was unresponsive to his environment during them. He sought evaluation for these events with his primary care pediatrician and was diagnosed with night terrors with no specific intervention recommended. Six weeks before admission, the patient had an episode of limb shaking at home in the early morning hours. Emergency medical services was called, and he was found to have a point-of-care blood glucose (BG) of 32 mg/dL. En route to the ED, the patient received intravenous dextrose and BG responded to 140 mg/dL with termination of his seizure. In the ED, repeat BG was 43 mg/dL and critical values of insulin, C-peptide, and cortisol revealed elevated insulin and C-peptide with normal cortisol per an outside report that did not provide values. While in the ED, the patient's BG stabilized with enteral intake, he was nonurgently referred to pediatric endocrinology, provided with a home glucometer, instructed to avoid prolonged fasting, and instructed to

abstract

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Dr Beisang provided direct patient care, synthesized the relevant history, exam, and laboratory elements, and wrote the primary manuscript; Dr Forlenza provided direct patient care, assisted with synthesis of history, exam and laboratory elements, and assisted with preparation of the manuscript; Dr Luquette provided direct patient care, assisted with discussion of the pathologic diagnosis, and assisted with preparation of the manuscript; and Dr Sarafoglou provided direct patient care, provided mentorship to Drs Beisang and Forlenza in preparation of the manuscript, and assisted with its preparation and revision.

DOI: https://doi.org/10.1542/peds.2016-2007

Accepted for publication Dec 2, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Forlenza is a consultant for Abbott Diabetes care and conducts research sponsored by Medtronic Diabetes; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Beisang D, Forlenza GP, Luquette M, et al. Sporadic Insulinoma Presenting as Early Morning Night Terrors. *Pediatrics.* 2017;139(6):e20162007

TABLE 1 Critical Laboratory Values

Laboratory Test	Value	Reference Range
Sodium (mmol/L)	140	133–144
Potassium (mmol/L)	3.7	3.4–5.3
Chloride (mmol/L)	106	98–110
Carbon dioxide (mmol/L)	26	20–32
Urea nitrogen (mg/dL)	10	7–21
Creatinine (mg/dL)	0.63	0.50–1.00
Glucose (mg/dL)	41	70–99
Calcium (mg/dL)	9.1	9.1–10.3
Albumin (g/dL)	4.2	3.4–5.0
Protein total (g/dL)	8.2	6.8–8.8
Bilirubin total (mg/dL)	0.3	0.2–1.3
Alkalinephosphatase (U/L)	195	65–260
ALT (U/L)	35	0–50
AST (U/L)	31	0–35
Insulin (uIU/L)	21	0-17
C-peptide (ng/mL)	3.7	0.9–6.9
Growth hormone (μg/L)	9.0	0–0.8
IGF-1 (ng/mL)	253	208–619
IGF-BP3 (μg/L)	2.6	3.2–9.2
Ketone qualitative (mmol/L)	0.1	0.0–0.6
Lactic acid (mmol/L)	0.9	0.4–2.0
Serum cortisol (μg/L)	4.7	4–22

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IGF-1, insulin-like growth factor 1; IGF-BP3, insuline-like growth factor binding protein 3.

consume complex carbohydrates before bedtime. Notably, pediatric endocrinology was not contacted during this initial ED encounter.

Over the subsequent 8 weeks, the patient consumed barley shakes before bedtime, and his mother woke him overnight each night for additional feedings of complex carbohydrates. Despite these interventions, his morning BG measurements were consistently in the 30s to 50s.

There was no known family history of cancer or autoimmune diseases, although little is known regarding the paternal lineage.

During evaluation in the pediatric endocrine clinic 8 weeks after the ED visit, the patient was asymptomatic, although he appeared thin and pale. His exam was otherwise unremarkable with no goiter, skin lesions, hepatosplenomegaly, or other abdominal masses appreciated. At arrival, his BG was found to be 41 mg/dL despite not fasting for the visit, and critical laboratories were immediately obtained (Table 1) showing a confirmed serum glucose level of 41 mg/dL, a C-peptide level of 3.7 ng/mL (reference: 0.9–6.9 ng/mL), an insulin level of 21 uU/mL (reference: 0–17 uU/mL), and a growth hormone level of 9.0 μg/L (reference: 0.0–0.8 μg/L). Given these findings, the patient was diagnosed with a hyperinsulinemic hypoglycemia of unknown etiology and admitted for additional management and diagnostic evaluation.

An abdominal MRI with and without intravenous contrast was performed (Fig 1A) to investigate for potential abdominal mass, however, this imaging revealed a "normal appearing liver and biliary system, spleen, and pancreas." In the hospital, the patient maintained euglycemia for >24 hours with oral feedings every 2 hours and complex carbohydrate administration at bedtime. After the patient's MRI, he was discharged from the hospital with a plan to continue his inpatient feeding regimen as an outpatient. Before discharge, diazoxide was discussed as a medication option for blood glucose management, however, the patient's mother declined this medication due to concern for insurance coverage and potential side effects (peripheral edema, hirsutism, and weight gain).[4]

An outpatient endoscopic ultrasound (EUS) was performed (Fig 1B) to investigate for possible pancreatic tumor and revealed "a pancreas with diffusely abnormal parenchyma, which was hyperechoic with honeycombing nodularity more pronounced in the tail." Additionally, a 16 × 10 mm lobular/triangular mass in the uncinate process of the pancreas was identified that was "hyperechoic and homogeneous." Fine-needle aspiration of this mass was performed under endoscopic ultrasound guidance (Fig 1C and D) and revealed pathologic findings consistent with a pancreatic neuroendocrine tumor.

The patient ultimately underwent exploratory laparotomy and pancreaticoduodenectomy secondary to the close proximity of the mass to the pancreatic duct and portal vein. Postoperative recovery was uncomplicated, and the patient remained euglycemic over a 12-hour fasting period and was subsequently able to maintain his BG with a regular diet. Surgical pathology was consistent with a well-differentiated, insulin-secreting neuroendocrine tumor. Given the benign features and low likelihood of metastatic disease, no postoperative chemotherapy or radiation was recommended.

Given the association of insulinomas with multiple endocrine neoplasia type 1 (MEN-1)[5], the patient was screened for pituitary and parathyroid adenomas with insulin-like growth factor 1, prolactin, and parathyroid hormone, and all were found to be within normal limits. Gene sequencing of the *CDKN1B* and *MEN1* genes was negative, suggesting an isolated insulinoma not part of MEN1 syndrome. At follow-up 7 months after surgical resection,

the patient was stable with no hypoglycemic events since resection.

DISCUSSION

Insulinoma is a rare neuroendocrine tumor derived from the insulin-producing β cells of the pancreas. This tumor has an incidence of 0.4% and occurs sporadically ∼90% of the time, but in 5% to 10% of cases it is associated with MEN-1 syndrome[1]. The vast majority (90%) of these tumors are nonmalignant in nature and have excellent prognosis, however, MEN-1–associated tumors have a tendency toward a more malignant phenotype.[6] The tumor in this case was a non–MEN-1 syndrome–associated tumor based on genetic sequencing of the *CDKN1B* and *MEN1* genes from peripheral blood samples.[7–9]

Diagnosis of insulinoma is classically made through identification of the Whipple triad, which includes (1) signs/symptoms typically associated with hypoglycemia, (2) documentation of low plasma glucose at the time of these symptoms, and (3) relief of symptoms after administration of glucose. The patient fulfilled Whipple criteria with his hypoglycemic seizure, which stopped on administration of glucose; however, during his initial hospitalization he had multiple documented hypoglycemic periods without report of any symptoms suggestive of hypoglycemia. Hypoglycemia unawareness is thought to be a result of failure of the physiologic epinephrine-mediated sympathetic response to hypoglycemia through incompletely understood mechanisms.[10] It is likely that the patient's hypoglycemic unawareness was due to frequent hypoglycemic episodes for an extended period of time before presentation.[11]

This case, along with previously published case reports, highlights the importance of maintaining a high index of suspicion for hypoglycemia in patients who develop altered mentation (such as night terror–like events) or other signs of hypoglycemia,[12,13] particularly in the early morning hours after a night of sleep. The difficulty in making this diagnosis is highlighted by the average prolonged time to diagnosis, with 1 study demonstrating a median of 24 months from the onset of symptoms to diagnosis.[14] One of the keys to the diagnosis of insulinoma is the acquisition of a critical sample for diagnostic testing. The critical sample should be obtained in any patient fulfilling the Whipple triad or in younger children or infants ≥48 hours of age with a serum glucose measurement below that expected to trigger neurogenic symptoms (∼55 mg/dL). The critical sample should be obtained before glucose administration and include measurement of serum glucose, electrolytes, free fatty acids, serum ketones, and plasma insulin with extra serum held in reserve for additional specific testing. Pediatric endocrine consultation should be initiated while the patient is in the ED. When interpreting the critical sample, one should keep in mind that laboratory reference ranges may not be applicable in the setting of hypoglycemia.[15]

Radiologic imaging of insulinomas remains a challenging and evolving diagnostic dilemma. Commonly employed imaging modalities include contrast-enhanced computed tomography, MRI, and EUS. On review of the available data, EUS appears to be the procedure of choice in terms of both increased sensitivity to lesions below the size limit of MRI identification, as well as the ability to simultaneously obtain biopsies for tissue diagnosis, as was performed in this case.[1,16,17] The modality of choice will likely change, however, as the performance of noninvasive imaging modalities increases. A retrospective

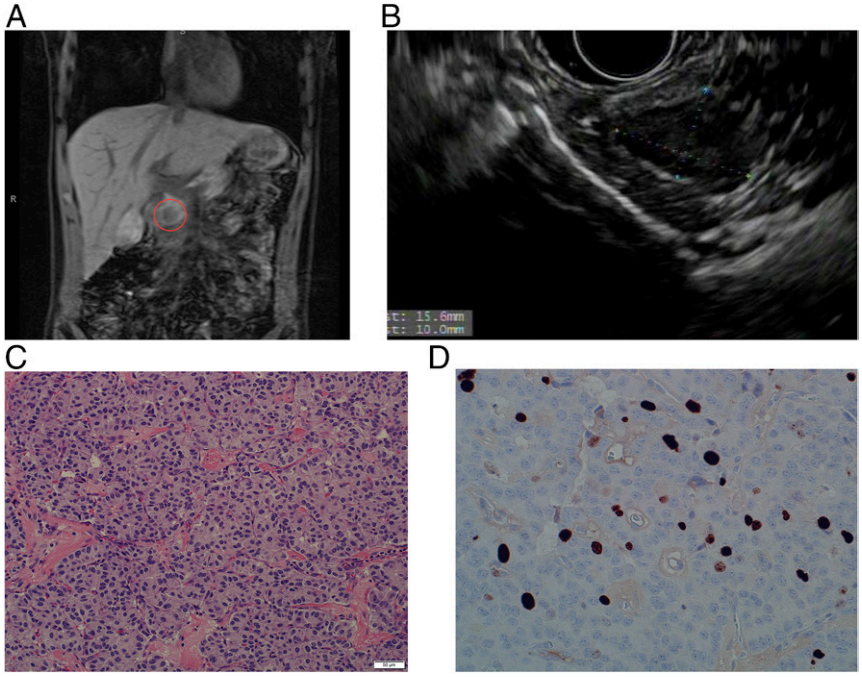

FIGURE 1

A, Sagittal view of noncontrast abdominal MRI showing a hypointense lesion in the head of the pancreas. B, EUS showing a 1.6-cm × 1.0-cm lesion in the head of the pancreas. C, Photomicrograph showing the typical histology of an islet cell tumor with nests and festooning bands of cells with islet cell morphology. Scale bar represents 50 microns. D, This Ki-67 immunohistochemical stain documents the elevated proliferation index of this intermediate-grade tumor.

review of our patient's abdominal MRI did reveal a 2.2-cm lesion in the head of the pancreas, consistent with the insulinoma identified by EUS, but likely not appreciated on initial review due to the rarity of this lesion.

The management of insulinomas can be both medical and/or surgical. The majority of insulinomas are managed successfully through surgical excision.[18] Medical management of insulinomas is often reserved for situations of palliation until definitive surgical management or for tumors deemed inoperable.[6] Medical management consists of frequent enteral feedings with complex carbohydrates, such as uncooked cornstarch[2] and diazoxide. Diazoxide increases cell-membrane potassium permeability, thus turning off voltage-gated calcium channels and subsequently decreasing insulin secretion from pancreatic β cells.[19] A diazoxide-mediated decrease in insulin secretion is moderately effective, controlling hypoglycemia in 50% to 60% of patients.[20] Despite symptom management with medical therapy, surgical excision remains the mainstay of therapy. Resection of the tumor and immediately surrounding tissue (enucleation) is the most commonly employed surgical intervention for insulinomas due to their overwhelmingly benign nature and small size (frequently <2 cm in greatest diameter) at presentation [6]. Pancreatectomy is often reserved for lesions that are concerning for malignancy, involving local structures or regional lymph nodes.[6]

Insulinoma is a rare pancreatic neuroendocrine tumor with quite variable presenting symptoms, but it is ultimately curable and typically has an excellent prognosis with surgical excision. The key to making this diagnosis is including hypoglycemia in the differential diagnosis when presented with atypical presentations of new-onset or worsening seizures or night terrors.

For pediatricians, it is important to be mindful of this differential and to obtain critical laboratory samples in the setting of unexpected or extreme hypoglycemia for subsequent diagnostic evaluation.

ABBREVIATIONS

BG: blood glucose
ED: emergency department
EUS: endoscopic ultrasound
MEN1: multiple endocrine neoplasia type 1

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Pediatrics 2017;139;
DOI: 10.1542/peds.2016-2007 originally published online May 24, 2017;

PEDIATRICS®
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