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Case report

Insulinoma Associated with MEN1 Syndrome: A Case of Persistent Hypoglycemia in School-aged Child

Lemus-Zepeda R et al. Insulinoma Associated with MEN1 Syndrome

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What is already known on this topic?
Insulinoma is a rare cause of non-ketotic hypoglycemia in pediatrics, mostly isolated benign lesions, but can also be part of a multiple endocrine neoplasia type 1 syndrome (MEN1).

What does this study add?
This case highlights that insulinoma can be the first manifestation of MEN1 syndrome, as in our patient, in whom a likely pathogenic variant in the *MEN1* gene was found, not previously reported in the literature.

ABSTRACT
Insulinoma is a rare cause of non-ketotic hypoglycemia both in adults and in children. Pediatric patients account for approximately 5% of all cases, mostly due to isolated benign lesions, but it can also be part of a multiple endocrine neoplasia type 1 syndrome (MEN1). We report the case of a patient with multiple hospitalizations related to hypoglycemia and neuroglycopenia symptoms, with multiple studies demonstrating the presence of an insulinoma as part of the spectrum of MEN1 syndrome. The primary significance of our report is to underscore that insulinoma can present as the initial manifestation of MEN1 syndrome in 10% of pediatric patients. Furthermore, we describe a likely pathogenic variant in the *MEN1* gene not previously reported in the literature. Our report highlights the importance of the convergence of clinical, biochemical and molecular investigations in establishing a precise diagnosis, prognosis, and appropriate follow-up for pediatric patients with hypoglycemia.
Keywords: hypoglycemia, insulinoma, pediatrics, MEN1 syndrome.

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INTRODUCTION
Hypoglycemia is the most common metabolic disorder in childhood (1). It is universally defined as a plasma blood glucose concentration low enough to cause signs and symptoms of impaired brain function (2) and cannot be defined as a specific concentration because brain response thresholds are individual, and the injury extent is influenced by the duration and degree of hypoglycemia (3). However, it has been shown that neurogenic symptoms are perceived at a plasma glucose concentration <55 mg/dL (<3.0 mmol/L), and at <50 mg/dL (<2.8 mmol/L) it disrupts cognitive function (neuroglycopenia) (3). The serum glucose level that defines hypoglycemia remains controversial (1), with the American Association of Pediatrics (AAP) defining hypoglycemia as a blood glucose level of <47 mg/dL (2.61 mmol/L]) and the Pediatric Endocrine Society (PES) suggesting a blood glucose level of <50 mg/dL (2.77 mmol/L) (4). Its incidence is inversely proportional to age, given the higher glycemic demands in the first two years of life (3).
The etiology of hypoglycemia is broad and varies with age. It includes low food intake, metabolic disorders of endocrine origin, medications, inborn errors of metabolism, iatrogenesis, and tumors, including insulinoma (3).
With an incidence of three cases per million adults, which peaks between the third and sixth decades (5), insulinoma is a rare tumor in children and adolescents (6,7). In the pediatric age group, 90% are single benign tumors; the remaining 10% are usually multiple, malignant, and generally associated with the multiple endocrine neoplasia type 1 syndrome (MEN1). Early diagnosis is essential for the prevention of irreversible neurological lesions. In the case of MEN1, it is also important to monitor and follow the development of other associated endocrinopathies for timely treatment.
Here we present the clinical case of a schoolboy with multiple hospitalizations related to hypoglycemia and neuroglycopenic symptoms, in whom an intrapancreatic insulinoma was diagnosed. Given the patient's age, a molecular study was performed, which revealed a likely pathogenic variant in the *MEN1* gene not previously reported in the literature, thus confirming the diagnosis of MEN1 syndrome.

CASE PRESENTATION
An eight-year-old boy presented with a two-year history of episodes described by his mother as "increased sleepiness" mainly in the morning; later associated with irritability, loss of tone and episodes of disconnection with apparent abnormal movements and, occasionally, relaxation of the urinary sphincter, and likely postictal phase. The etiological study documented an echocardiogram, Holter electrocardiogram (ECG), tilt table test, simple cranial computed tomography (CT), and an electroencephalogram, all unremarkable.
He was hospitalized when hypoglycemia was documented during an episode of abnormal movements. At the referral center he had two critical samples, reporting non-acidotic, non-ketotic hypoglycemia and detectable insulin levels, with an insulin/glucose ratio of less than 0.3, in addition to normal lactate, ammonium, cortisol, and growth hormone levels. Additionally, reports of a contrast-enhanced abdominal CT scan and a contrast-enhanced abdominal magnetic resonance imaging (MRI) were both unremarkable. He was transferred for further evaluation.
At admission to our centre, besides the above-mentioned, his personal and family medical history and physical exam were all unremarkable. His weight was 1.3 SDS, height 1.5 SDS and body mass index 0.7 SDS.

Fatty acid profile testing was not performed due to restrictions on the shipment and processing of international referral tests during COVID-19 lockdown. Due to a possible beta-oxidation of fatty acids defect, specifically medium-chain triglycerides, dietary management was initiated, without a complete weaning from intravenous glucose infusion rate.
After fasting for 5 hours and without intravenous dextrose infusion, a new critical sample was obtained, with evidence of hyperinsulinemic non-ketotic hypoglycemia [plasma glucose 33.5 mg/dL, negative serum ketone bodies, insulin 13.3 µUI/mL (2.6-24.9)], and glucose elevation after glucagon administration (response at 10 minutes, 71 mg/dL and at 20 minutes, 98 mg/dL). A thorough review of medication use suggestive of Hirata syndrome was negative; there was no evidence of surreptitious use of insulin-type medications or sulfonylureas. There were no findings suggestive of overgrowth syndromes associated with hypoglycemia (8).
A C-peptide level of 2.9 ng/mL (1.1-4.4 ng/mL) and the elevated C-peptide/glucose ratio suggested endogenous hyperinsulinemia, so a new contrasted abdominal MRI was performed, which showed an image consistent with an insulinoma in the uncinate process of the pancreas (Image 1). Enucleation by laparotomy was performed. Pathology revealed a well-differentiated neuroendocrine pancreatic tumor measuring 2.7 x 2.2 x 1.6 cm and weighing 4.6 grams, negative for vascular or perineural invasion. Immunohistochemical staining showed positivity for chromogranin, and weak homogeneous positivity for the insulin immunolabel in the tumor cells (image 2). This result confirmed the diagnosis of insulinoma.
The patient had a satisfactory course with remission of symptoms, and normalization of glycemia. Calcium, phosphorus, parathyroid hormone (PTH), prolactin, and insulin-like growth factor 1 (IGF-1) levels did not suggest associated endocrinopathies.
Given the low frequency of insulinomas in children, it was evaluated by the medical Genetics service. A single clinical exome was performed, with evidence of a variant in the *MEN1* gene (NM_001370259.2) c.1121delA p.(Asn374Thrfs*3) in heterozygosis, classified as likely pathogenic according to ACMG criteria (9), not previously reported in the literature. Family history for MEN1 syndrome was negative. The patient continues endocrine and genetic follow-up close to his home; two years after the insulinoma resection, he remains normoglycemic and under surveillance for related endocrinopathies.

DISCUSSION

Insulinoma is a neuroendocrine tumor from the insulin-producing pancreatic beta cells, causing hyperinsulinemia (8). It is suspected when documenting hypoglycemia using the Whipple triad (neuroglycopenic symptoms, biochemical hypoglycemia, and reversal of symptoms after carbohydrate ingestion) (3), and fulfilling criteria for hyperinsulinemic hypoglycemia, which include: plasma glucose <50 mg/dL, detectable insulin levels, C-peptide≥0.5 ng/mL, beta-hydroxybutyrate <2mmol/L, glycemic response to glucagon ≥30 mg/dL, low free fatty acids, and negative blood sulfonylurea levels (2).
Insulinoma is a rare pediatric tumor (6). A study that analyzed insulinoma cases over 60 years showed that pediatric patients accounted for 5.8% of all cases, with no gender predilection (10). Most insulinomas originate in the pancreas (98%). Approximately 90% are benign, unifocal lesions, smaller than 2 cm, uniformly distributed throughout the pancreatic structure. The remaining 10% are usually multifocal and malignant (10).
Preoperative localization includes imaging studies such as endoscopic ultrasound, MRI, and CT; functional studies such as DOTATATE PET-CT, glucagon-like peptide 1 (GLP1) receptor scintigraphy; or more invasive techniques such as celiac trunk angiography, selective intra-arterial stimulation, and intraoperative pancreatic ultrasound (2). Abdominal MRI is a reasonable starting study. Insulinomas can be characterized by immunohistochemistry, but no clear histopathologic parameters or histochemical markers predict tumor behavior (6, 11). Surgery is the mainstay of insulinoma treatment, with a remission rate ranging from 77% to 100% (5).
Insulinoma can be sporadic or associated with MEN1 syndrome, which represents about 4% of insulinomas (12). MEN1 syndrome (OMIM 131100) is an autosomal dominant disorder caused by mutations in the *MEN1* gene. It is characterized by endocrine and non-endocrine tumors. The main endocrinopathy in MEN1 is parathyroid tumors, present in 90% of patients by age 50, followed by pituitary tumors in 30-40% of patients (prolactinoma being the most common), and gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including gastrinoma (40%), insulinoma (10%), glucagonoma (<3%). Associated tumors include adrenal cortex tumors (40%) and pheochromocytoma (<1%), among others (13).
The *MEN1* gene is located on chromosome 11q13, (14) and consists of 10 exons; it encodes for a 610 amino acid protein called menin. Although, its specific function is yet to be established, it has been shown to interact with proteins related to transcriptional regulation, genomic stability, proliferation, and cell division (15). Approximately 1,133 germline mutations in the *MEN1* gene have been reported (13), the most frequent being frameshift mutations (40%), as in our patient, followed by nonsense mutations (23%), missense mutations (20%), mutations in the splicing site (9%), deletions/ insertions without reading frame alteration (6%) and large deletions in 1%; loss-of-function variants represent 75% of these mutations (15). *MEN1* is a tumor suppressor gene with increased risk of developing neoplasms when mutated. MEN1 syndrome has a prevalence of approximately 1 in 10,000 to 100,000 individuals, varying by geographical region. It is more prevalent in Finland due to a founder effect (16). The penetrance reaches 95% by 40 years of age (17). Currently, no genotype-phenotype correlation has been identified (18).
In 10% of patients, insulinoma is the first manifestation of MEN1 syndrome, typically before age 20, and presenting with symptomatic fasting hypoglycemia (13). MEN1-associated insulinomas tend to be larger than 1 cm and can be multiple in about 30% of MEN1 patients (19). MEN1-associated insulinomas in children have a higher risk of metastasis in approximately 50% of cases; whereas in patients without MEN1, insulinomas occur after the age of 40 and metastasize in only 10% of cases (13).

Padidela et al. (20) described a series of nine pediatric patients, including two with MEN1 syndrome. Both cases exhibited insulinoma as the first endocrinopathy, with one later developing a parathyroid adenoma. Bhatti et al. (21) reported 12 patients aged between 4 to 16 years, with 5 displaying clinical and molecular features of MEN1 syndrome, one patient presenting with insulinoma as the first endocrine manifestation, and none having parathyroid adenoma. These series indicate a higher frequency of MEN1-associated insulinoma in children compared to adults and emphasize the importance of performing molecular studies to clarify the diagnosis, due to its implications for continuous follow-up and surveillance. None of the previously reported cases had the variant presented in our case. The report of new variants is beneficial to establishing a genotype correlation for future cases.

CONCLUSION

The patient presents with an insulinoma as part of MEN1 syndrome spectrum, with a likely pathogenic variant in the *MEN1* gene, not previously reported in the literature. Insulinoma is a rare cause of non-ketotic hypoglycemia in pediatrics. Due to the higher frequency of MEN1-associated insulinoma in children compared to adults, it is advisable to perform genetic testing in all pediatric patients with insulinoma, as insulinoma can be the first manifestation of MEN1. These patients will require clinical follow-up and continuous monitoring due to the risk of developing other tumors and endocrinopathies associated with MEN1.

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Image 1: Abdominal MRI
Oval solid mass with well-defined borders, 2.5 x 1.5 cm, hypervascular in the uncinate process of the pancreas, compatible with insulinoma by imaging features and clinical presentation

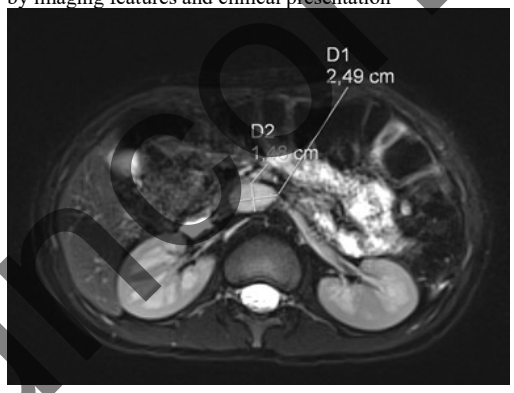

Image 2: Histology of Insulinoma
Immunohistochemical staining with antibodies against insulin, glucagon, chromogranin A and B, and keratins; positive to keratin and weak to insulin in ductal cells. Cell proliferation marker KI67 of 2%, compatible with insulinoma.