Insulinoma: Un diagnóstico infravalorado de hipoglucemia en pacientes de edad avanzada

Insulinoma: An undervalued diagnosis of hypoglycemia in elderly patients

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ABSTRACT

Insulinoma is a rare pancreatic endocrine tumor, characterized by the inappropriate secretion of insulin, leading to episodes of hypoglycemia. During these hypoglycemic events, patients may experience autonomic and neuroglycopenic manifestations. However, it is important to note that insulinoma can also have long-term effects on cognitive function, even after hypoglycemia resolution.

We present the case of an 89-year-old female with a gradual cognitive decline two years prior and recurrent episodes of stuporous level of consciousness in the preceding months. Insulinoma was confirmed through the measurement of plasma glucose, insulin, and C-peptide levels. Following the biochemical confirmation, a computed tomography (CT) scan successfully located the tumor. Surgical resection was considered high-risk. Nevertheless, after dietary modifications and the administration of diazoxide, the patient's hypoglycemic episodes were controlled.

This case report highlights the importance of considering insulinoma as a potential cause of unexplained episodes of hypoglycemia, particularly in older patients with cognitive impairment.

Keyword: Insulinoma, hypoglycemia, cognitive impairment, diazoxide.

RESUMEN

El insulinoma es un tumor endocrino pancreático poco común, caracterizado por la secreción inadecuada de insulina, lo que lleva a episodios de hipoglucemia. Durante estos eventos de hipoglucemia, los pacientes pueden experimentar manifestaciones autonómicas y neuroglucopénicas. Es importante señalar que el insulinoma también puede tener efectos a largo plazo sobre la función cognitiva, incluso después de la resolución de la hipoglucemia.

Presentamos el caso de una mujer de 89 años con deterioro cognitivo gradual dos años antes y episodios recurrentes de nivel de conciencia estuporoso en los meses anteriores. El insulinoma se confirmó mediante la medición de los niveles plasmáticos de glucosa, insulina y péptido C. Tras la confirmación bioquímica, una tomografía computarizada (TC) localizó con éxito el tumor. La resección quirúrgica se consideró de alto riesgo. Sin embargo, tras modificaciones dietéticas y la administración de diazóxido, se controlaron los episodios de hipoglucemia del paciente.

Este caso destaca la importancia de considerar el insulinoma como una causa potencial de episodios inexplicables de hipoglucemia, particularmente en pacientes mayores con deterioro cognitivo.

Palabras clave: Insulinoma, hipoglucemia, deterioro cognitive, diazóxido.

INTRODUCTION

Insulinomas are pancreatic endocrine tumors, characterized by an inappropriate secretion of insulin[1]. They are a rare disorder, with an estimated incidence of 4 cases per 1 million person-years and are more common in women during the fifth or sixth decade of life[2]. While most occur sporadically, approximately 10% of cases are associated with Multiple Endocrine Neoplasia type 1 (MEN-1) syndrome and typically manifest in the second decade of life[3]. Sporadic insulinomas are usually solitary, benign, and less than 2 cm in size.[4]

Symptoms can include both autonomic and neurological manifestations[2]. Due to the rarity of insulinomas and their nonspecific symptoms, it can take months to several decades before the diagnosis is made.[4] This delay leads to repeated and prolonged episodes of hypoglycemia, resulting in neurological deficits, explaining why most patients with insulinoma present cognitive impairment at the time of diagnosis.[5,6]

CLINICAL CASE

An 89-year-old female was assisted at home by the pre-hospital emergency team due to an episode of stuporous level of consciousness. In the previous four months, she was consulted by a general practitioner multiple times for similar episodes, all of which were associated with hypoglycemia and resolved after glucose administration. According to family members, the patient had become increasingly dependent on others due to a gradual cognitive decline that began two years earlier. No other prior medical or family history was known.

Emergency responders found the patient unresponsive with a capillary blood glucose measurement of 46 mg/dL. Oral glucose (25g) was administered, and she was then transported to the hospital emergency department. On admission, the patient had a capillary blood glucose measurement of 32 mg/dL, and a Glasgow Coma Scale (GCS) score of E1V1M4. After 50 mL of 50% dextrose in water was administered, the patient becoming responsive (GCS score of E4V4M6), with a blood glucose level of 93 mg/dL. Heart rate was 84 beats/minute and regular, blood pressure was 139/72 mmHg, and transcutaneous oxygen saturation was 96% without supplementary oxygen. At the physical examination no abnormalities were detected.

The patient was admitted to the Internal Medicine department for further evaluation. Laboratory investigations revealed a low glycated hemoglobin level (HbA1c of 4,2%) as the only abnormal finding. Ad-

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renal insufficiency and hypothyroidism were excluded due to normal morning cortisol levels (19.4 µg/dL) and thyroid-stimulating hormone (1.86 µUI/mL).

Endogenous hyperinsulinism caused by an insulinoma was suspected and a 72-hour fasting trial was initiated. At the eight-hour, the patient presented with an altered mental status, leading to the discontinuation of the fasting trial. During this episode, laboratory investigations suggested the diagnosis of insulinoma as they revealed hypoglycemia, a normal insulin and β-hydroxybutyrate levels, and a high C-peptide level (Table 1). An abdominal CT scan with contrast was able to locate the tumor, revealing a single hypervascular nodular lesion at the head of the pancreas measuring 10 mm (Figure 1). The absence of laboratory findings indicating parathyroid or pituitary involvement ruled out the possibility of MEN-1 syndrome (PTH 48.5 pg/mL; ACTH 21.3 pg/mL; prolactin 11.74 ng/mL).

Due to the considerable surgical morbidity and mortality and considering the patient's status as a high-risk candidate for surgery, medical therapy was chosen as the preferred approach. She was initiated on diazoxide 100 mg every 11 hours, along with dietary therapy to prevent prolonged periods of fasting. No more hypoglycemic episodes were registered, and the patient was discharged from the hospital. She was referred to an endocrinology consultation for further management and follow-up.

DISCUSSION

Most of hypoglycemic symptoms are caused by neuroglycopenia because the brain is incapable of storing or synthesizing glucose. They include confusion, behavioral changes, personality changes, visual disturbances, seizures, and coma[2]. There is also a risk of subsequent cognitive impairment and dementia because acute hypoglycemia impairs brainstem and hippocampal function, leading to deleterious effects on brain structure and memory function, even when blood glucose has returned to the normal range[6]. Recurring hypoglycemic episodes can also lower the glycemic threshold for the neurogenic response, resulting in hypoglycemia unawareness[7]. This can lead to hypoglycemic events for years before diagnosis, exacerbating cognitive impairment and dementia. A study found that 53% of patients with insulinoma screened positive for cognitive impairment even in situations without hypoglycemia. However, 70% of patients recover normal cognitive function one year after surgery.[6]

The diagnosis can be challenging, but the gold standard is the 72-hour fasting trial. During this trial, blood samples are taken when the patient develops symptoms. The diagnosis is then definitively established using six criteria:

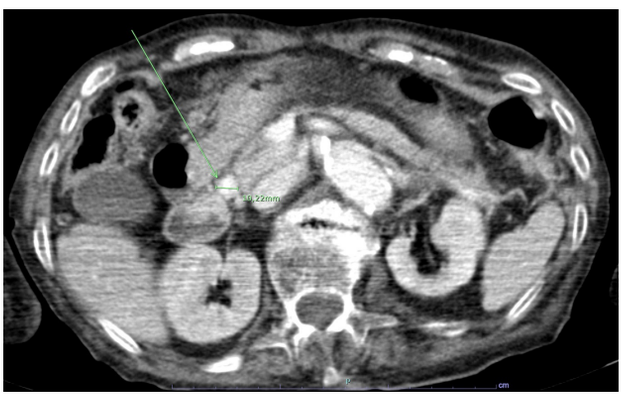
1. blood glucose ≤ 40 mg/dL;
2. insulin ≥ 6 µUI/mL;
3. C peptide ≥ 0.6 ng/mL;
4. β-hydroxybutyrate ≤ 2.7 mmol/L;
5. proinsulin ≥ 5 pmol/L;
6. absence of sulfonylurea metabolites in the plasma and/or urine.[8]

Our patient fulfilled 4 out of the 6 criteria for diagnosis. The other two criteria were not met due to inability of our hospital laboratory to measure proinsulin and sulfonylurea metabolites.

Table 1. Laboratory investigations during the 72-hour fasting trial.

Parameter	Results (normal range)
Glucose	30 (60-100 mg/dL)
Insulin	8.5 (3.0-35.0 µUI/mL)
C peptide	5.2 (0.8-4.0 ng/mL)
β-hydroxybutyrate	1.2 (≤ 2.7 mmol/L)

Figure 1



Surgical resection is the definitive treatment for insulinomas, while medical management is acceptable in inoperable patients[9]. Diazoxide is considered the most effective drug as it inhibits insulin release from the β-cells by stimulating α-adrenergic receptors[4]. Although mild and well tolerated, the main side effects include edema, weight gain, renal impairment, and hirsutism[4,8]. In this patient, hypoglycemic episodes were successfully controlled with dietary modifications and diazoxide, without significant side effects from the medication.

In conclusion, although we cannot prove that patient dementia was caused or worsened by the delay in diagnosis, hypoglycemic events prompt several medical evaluations months before diagnosis was considered. Therefore, physicians should consider insulinoma as a potential cause of unexplained episodes of hypoglycemia, particularly in older patients, to prevent further cognitive impairment.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interests.

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ETHICAL ASPECTS
All participants submitted a consent form to be included in this study.

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