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CASE REPORT

Insulinoma as a rare cause of hypoglycemia in childhood: case report

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Abstract

Introduction: Insulinoma is a neuroendocrine tumor that originates in pancreatic beta cells, resulting in severe and frequent preprandial hypoglycemia. The diagnosis should be considered in the presence of the Whipple triad (present in 75% of cases) and confirmed through the demonstration of high insulin levels associated with low serum glucose levels. Treatment is surgical and, in most cases, curative. **Case Report:** Girl, 10-years-old, hospitalized for the investigation of possible refractory epilepsy with predominant morning seizures, which started 6 months prior to her admission. A pediatric endocrinology evaluation was requested, as hypoglycemia was evidenced during the occurrence of seizures, which improved after intravenous glucose infusion. During the tests of the critical sample, hyperinsulinism associated with hypoglycemia was revealed. The diagnosis of insulinoma was therefore considered and then confirmed, after an intrapancreatic lesion showed up on the imaging tests. She was referred for surgical excision and had good evolution after tumor enucleation. **Comments:** Insulinoma is a rare neuroendocrine tumor in the pediatric group. It may initially present itself as a hard-to-control convulsive condition, accompanied by behavioral changes and developmental delay, which often leads to misdiagnosis. Thus, early diagnosis and intervention are important since they reduce the morbidity and mortality of affected individuals. The patient did not present neurological sequelae and had a favorable post-surgical evolution, without recurrence of symptoms or further episodes of hyperglycemia.

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INTRODUCTION

Insulinoma is an insulin-producing neuroendocrine tumor originating from pancreatic beta cells. Its incidence is believed to be 4:1,000,000 per year, with a predominance in females (2:1); it can occur in all ethnic groups. The mean age of presentation is 45 years old, which is rare in the pediatric age group[1].

Normally, these tumors are functioning and, due to the exuberance of the symptoms, the diagnosis is usually elucidated when their dimensions are still small, with an average time between the onset of symptoms and diagnosis of two years[2,3].The main manifestations are related to neurovegetative and neuroglycopenic symptoms secondary to hypoglycemia[4]. Up to 20% of patients are initially diagnosed with a neurological or psychiatric disorder.[2] In most cases, they are single, benign tumors. It can be found alone or as part of the multiple endocrine neoplasia type 1 (MEN-1) syndrome[1,5].

The diagnosis should be suspected in the presence of Whipple's triad (blood glucose < 50 mg/dL induced by fasting or after physical activity and rapid resolution of complaints after glucose administration). Confirmation should consider under high insulin levels in the presence of hypoglycemia and tumor location through imaging tests[1]. The treatment of insulinoma is performed through surgical excision, most often curative (77 to 100%), with enucleation of the tumor - the procedure of choice in cases of benign and solitary lesion[5]. If there is a contraindication for surgery or to relieve symptoms, drug treatment (diazoxide, verapamil and octreotide) may be indicated[4].

The aim of this paper is to report a rare case of insulinoma in the pediatric age group, with a favorable clinical outcome after surgical treatment.

CASE REPORT

A 10-year-old female patient was admitted to a pediatric ward for investigation of recurrent morning pre-prandial seizures. Six months ago, she had been diagnosed with epilepsy, after an abnormality in the electroencephalogram, being refractory to the use of anticonvulsant.

In the last convulsive episode, hypoglycemia was evidenced (capillary blood glucose: 33 mg⁄dL), with improvement after intravenous glucose infusion, and she was referred to this service for investigation of symptomatic hypoglycemia.

The patient's critical sample exams (plasma glucose: 35mg/dL) showed an inappropriate elevation of insulin levels (10.8 mcUI/mL), with no evidence of ketonemia and/or ketonuria. Abdominal tomography figura 1 showed two lesions, only visualized in the arterial phase, one in the head of the pancreas, measuring 1 cm, and another in the pancreas tail, measuring 0.9 cm. The patient underwent endoscopic ultrasound, which showed an isoechogenic nodule in the head of the pancreas, with no other evident lesions. Investigation was carried out for NEM-1. She had normal calcium metabolism exams and her head magnetic resonance imaging showed no evidence of pituitary lesions. She was unaware of a similar case in the family.

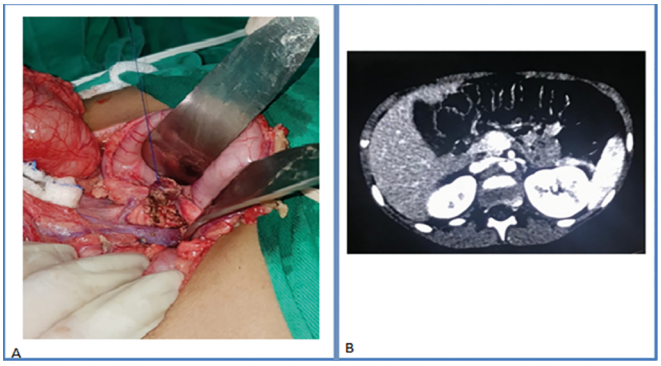


Figure 1. A. Intraoperative image of pancreatic insulinoma. **B.** Insulinoma on computed tomography of the abdomen.

The patient underwent laparotomy for enucleation of the lesion in the head of the pancreas, and the histopathological result was compatible with a neuroendocrine tumor. Her immunohistochemistry was positive for synaptophysin and chromogranin, and the Ki67 proliferation index was positive in 10% of the cells (grade II).

After the surgical procedure, there were no new episodes of hypoglycemia, as well as no hyperglycemia, allowing the patient to have an appropriate diet for her age. Glucose intolerance has not been demonstrated to date.

COMMENTS

Although rare, insulinoma is the most frequent pancreatic neuroendocrine tumor, causing hyperinsulinemia. About 73% of patients present symptoms of non-ketogenic hypoglycemia, exclusively in pre-prandial periods, similar to what was found in the patient in the case described[6,7].

These tumors can be distributed throughout the pancreas but are more common in the tail and body[2]. About 90 to 95% of insulinemic lesions in children are benign, although some may have malignant potential, with a malignancy incidence rate of 6%[8].

In children, insulinomas have a differential diagnosis of persistent hyperinsulinemic hypoglycemia, which has a higher incidence in children of Saudi or Jewish origin, with clinical manifestations of persistent hypoglycemia earlier (hours/days after birth). In contrast,

insulinomas are usually diagnosed after the age of four, but neonatal cases have already been reported in the literature[9].

The symptoms can be divided into neurological (neuroglycopenic) and adrenergic conditions. Diplopia, blurred vision, altered mental status, abnormal behavior, amnesia, coma, and seizures may be neurological symptoms. Symptoms caused by the adrenergic response include sweating, anxiety, palpitations, weakness, tremors and nausea[3,4,6]. The patient in the case had recurrent seizures that were refractory to drug treatment. Due to the young age of the patient, some complaints were difficult to describe as present.

According to the latest guidelines, the gold standard for diagnosing insulinoma is a 72-hour fasting test in a hospital setting, but for younger patients, some sources advise that 48 hours is sufficient. Diagnosis is based on the following laboratory criteria: documented blood glucose ≤40 mg/dL associated with insulin values ≥6 mU/L, C-peptide ≥200 pmol/L and proinsulin concentration ≥5 pmol/L.10[10]. In the case reported, the finding of hyperinsulinemia (10.8 mcUI/mL), in the presence of hypoglycemia (35mg/dL), confirms the diagnosis.

Despite the evolution in diagnostic methods, the location of insulinomas through invasive and non-invasive techniques remains a challenge, but it is extremely important, before the surgical approach, to decide on the best treatment. About 80% of insulinomas are smaller than 2 cm, so it is often not evident in preoperative imaging studies[1,3]. Although the child in the case reported had a lesion of only 1 cm and another of 0.9 cm, visualization by imaging examination was possible. Endoscopic ultrasonography has high sensitivity (80-85%) and specificity (95%) for diagnosis, but it is not always available in services. Currently, intraoperative ultrasound, when available, is considered the best method (90% sensitivity)[2,4].

Imaging tests associated with aspiration of material by fine or large needle with cytopathological analysis of the biopsy may be necessary to confirm the presence of a neuroendocrine tumor, identify metastasis to lymph nodes and determine the proliferation index (number of mitoses, Ki-67). Such conducts are important to establish the treatment, through the staging of the lesion[5].

In 2017, the World Health Organization (WHO) Guidelines were published, classifying tumors according to histological grade, pathomorphological system and clinical staging[11].The most important parameter of a tumor is its histological maturity, evaluated by the Ki-proliferative index.67 and its mitotic count. They are classified into well-differentiated tumors (Ki-67 < 20%) and poorly differentiated tumors (Ki-67 > 20%), in addition to a subcategory of large and small cell neuroendocrine carcinomas (NEC) characterized by an exceptionally aggressive course, and a subcategory of well-differentiated neoplasms with a Ki-67 proliferative index above 20% (NET G3) (Table 1)[10].

The treatment of choice is surgery, with a complete resection rate reaching 60%. The surgical approach chosen depends on tumor location, with laparoscopy being the preferred route in the case of tumors with known location - the method chosen for the child in the case described. Small, superficial tumors can simply be enucleated, without the need for partial pancreatectomy, due to the low rate of malignancy of insulinomas[3,4]. Recent studies show that, after resection, cure rates reach 87.5%; and 2.25% of patients develop diabetes. The survival of patients with benign insulinomas is not different when compared to the normal population, and the incidence of cumulative recurrence is 6% at 10 years and 8% at 20 years. Recurrence after four years of surgery is related to residual lesion growth[8].

The cure criteria for patients diagnosed with insulinomas after surgical resection are the disappearance of symptoms of hypoglycemia and the normalization of blood glucose levels, as occurred in the case reported.[4]

Insulinomas are rare in children. However, it is important to be aware of its symptoms, emphasizing that it can start with seizures, as in the patient described, and with behavioral disorders. Early diagnosis is necessary, so that appropriate treatment can be quickly instituted, in order to avoid sequelae and, consequently, improve the survival of these patients.

Table 1. WHO classification of pancreatic neuroendocrine neoplasms.

NET G1	NET G2	NET G3	NEC
Ki-67<3%	Ki-67<3-20%	Ki-67>20%	Ki-67>20%
Well differentiated	Well differentiated	Well differentiated	Somewhat differentiated; divided into small and large cell carcinomas
Mitotic index < 20⁄10 fields	Mitotic index 2 - 20⁄10 fields	Mitotic index > 20⁄10 fields	Mitotic index > 20⁄10 fields
Low malignancy	Medium malignancy	Less aggressive than the NEC	Extreme aggressiveness

NET = Neuroendocrine tumor; NEC = Neuroendocrine Carcinoma.

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