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Case report

Nesidioblastosis. A case of hyperplasia of the islets of Langerhans in the adult

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ABSTRACT

Introduction: Nesidioblastosis is a rare disease caused by hyperplasia of pancreatic islets, developing a state of hypoglycemia due to an increase in the insulin production. It is the leading cause of hyperinsulinic hypoglycemia in childhood, whereas in adults it only represents the 0.5–5% of cases.
The pathogenesis is still unknown. We have studied several genetic mutations associated with dependent potassium channel of ATP present in the beta cells of the pancreas, as well as in patients underwent bariatric surgery because of the metabolic changes involved.
Report: Woman (38 years old) attends consultation of General Surgery derived from Endocrinology before symptoms of persistent hypoglycemia. Factitious hypoglycemia and syndromes of neuroendocrine origin were ruled out. Imaging tests failed to identify space-occupying lesions. The medical treatment failed, persisting hypoglycemia symptoms. Before the given analytical and radiological findings obtained, and the persistence of symptoms affecting the quality of life of the patient, we opted for surgical treatment performing a pancreatectomy of the 80% of the gland. The final pathologic diagnosis was nesidioblastosis.
Discussion: Nesidioblastosis is a rare pathology, but it must be present in the differential diagnosis of hypoglycemia symptoms with endogenous hyperinsulinism in adults, once the intake of sulfonylureas and possible pancreatic neoformations have been ruled out.

1. Introduction

Nesidioblastosis is a rare illness that causes hypoglycemia and endogenous hyperinsulinism. In addition, Nesidioblastosis is caused by hyperplasia of the pancreatic islets. Most frequently, it occurs in childhood, unlike adults that only it represents 0.5–5% of cases of organic hyperinsulinism, becoming more common as causal pathology other lesions as insulinoma.

We report a woman (38 years old) with nesidioblastosis and we also review the previous literature.

2. Case report

Female patient of 38 years who attended a General Surgery derived from Endocrinology before symptoms of persistent hypoglycemia. Without personal or family history of diabetes mellitus. On the other hand, she was diagnosed of duodenal ulcer in 1995. However, with persistent clinical and despite the medical treatment, she was underwent surgery in 2003, performing a pyloroplasty and a truncal vagotomy by laparotomic access. Since the surgery, the patient had frequent episodes of hypoglycemia with adrenergic symptoms (dizziness, cold sweats, tremors), corroborated by reflectometer, reaching 20 mg/dl and without an improvement with dietary measures. These episodes were much more frequent in the postprandial period, although they also occurred outside.

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A test of fasting in 72 h and a mixed meal test were performed getting negative results for both of them. Besides, the urine analysis ruled out factitious hypoglycemia by surreptitious ingestion of sulfonylureas. The anti-insulin antibodies were also negative. A peripheral blood analysis showed: glucose of 43 mg/dl, insulin of 21.1 mU/ml and a C-peptide 7.4 ng/ml. Thyroid hormones and the cortisol were in normal limits, as gastrin, chromogranin A or Polypeptide pancreatic ruling out syndromes of neuroendocrine origin.

In the abdominal ultrasound scan, pathological finds were not found.

With the suspicion of an early *Dumping* syndrome without an improvement despite the conservative treatment, she was again operated performing an antrectomy and a "Y de Roux" reconstruction. After the second surgery, the patient continued presenting episodes of hypoglycemia with the same features as the previous ones, and she was diagnosed syndrome of hypoglycemia by non-insulinoma endogenous hyperinsulinism (NIPHS) and it was considered a treatment with Glucocorticoids and Somatostatin Analogs (Somatulina Autogel 60) for a month. Before the absence of an improvement, Somatulina was replaced by Calcium-antagonists and subsequently by Diazoxide, without observing any improvement in the clinical condition of the patient.

She was made a Computed Axial Tomography (CAT) without observing masses or suggestive finds of insulinoma and a test of intra-arterial Infusion of calcium with hepatic venous sampling of insulin which showed the diffuse nature of the disease, without observing local catchment areas in the pancreas. The study was completed with an Octreoscan in which there was no grammagraphic detection of lesions with somatostatin receptors.

Given the analytical and radiological findings obtained and the persistence of the symptoms that affected the quality of life of the patient, we chose surgical treatment. Under general anesthesia and on a scheduled basis and having identified the pancreatic gland, masses or lesions were not palpated nor observed by intraoperative ultrasound scan except for an area of approximately 15 mm in the pancreatic tail of a great heterogeneity. Given the diffuse nature of nesidioblastosis and recommendations of the literature, we decided to perform distal pancreatectomy, removing approximately 80% of the gland. After intra-arterial injection of calcium gluconate, venous samples insulin were obtained before and after pancreatic resection, aiming at a decrease of insulin and thus proving the efficiency of the operation.

In the postoperative period, the patient progressed favorably, keeping during all her admission, basal glycemia above 90 mg/dl.

In the pathologic study was objectified a macroscopically normal pancreatic gland. From the microscopy point of view, it was appreciated a hyperplasia of the islets of Langerhans with hypertrophy of the beta cells together with complex ductile-insulars. There were no malignancy areas on the piece; therefore the definitive diagnosis was nesidioblastosis.

Currently, 9 months after surgery, she is asymptomatic, keeping blood glucose within normal limits.

3. Discussion

The first time nesidioblastosis was described was in 1938 by George Laidlaw. This term comes from Greek "nesidion" which means islands and "blasts" referring to germination. Thus, Laidlaw defined a rare disorder resulting from neodiferentiation or neoformation of cells of the islets of Langerhans in exocrine pancreatic ductal epithelium. Initially, it was observed in newborns, even thought nesidioblastosis is now recognized as the main cause of hyperinsulinamic hypoglycemia in childhood.

The exact pathogenesis of nesidioblastosis has not been deciphered yet. About 95% of the cases in children are sporadic.

Diverse genetic alterations responsible for the hyperplasia of the pancreatic beta cells are known. The two affected genes are primarily: ABCC8 (SUR1) and KCNJ11 (Kir 6.2), which are responsible for encoding the potassium channel subunits sensitive to Adenosine Triphosphate (ATP) placed on the beta cell membrane. Mutations in these genes, which are located on chromosome 11p14-15.1, cause alterations in the channel favoring the inactivity of the same. Consequently, the closure causes the cell membrane depolarization and the calcium entry, which facilitates a continuous secretion of insulin [1,2]. The inappropriately high insulin levels promote hepatic glycogenesis in skeletal muscle reducing the free glucose in blood and lifting the formation of free fatty acids that act as brain substrate, so that adrenergic and neuroglycopenic symptoms proper of the state of hypoglycemia appear [3]. Most cases have an autosomal recessive inheritance. There is a less common form of autosomal dominant transmission that usually affects to GLUD1y GK genes and ATP/ADP relation in the beta cell [1,4].

In adults, however, the insulinoma is the main cause of hyperinsulinamic hypoglycemia, being nesidioblastosis a rare disease that only represents about 0.5–5% of cases [1]. Until the early 80's, in adults, it had always been described in the context of other syndromes or diseases such as Zollinger–Ellison syndrome, congenital neuroblastoma, chronic pancreatitis, cystic fibrosis and syndrome of Multiple Endocrine Neoplasia (MEN), among others. The first case of an adult nesidioblastosis was described in 1975 and from then, it has been published in the literature less than a hundred cases in the adult, sporadically, unrelated to other syndromes or diseases as a diffuse and heterogeneous dysfunction of the pancreatic beta cells, sporadic circumstance, since mutations have no been documented as in the cases in children [5–7].

On the other hand, in morbidly obese patients undergoing bariatric surgery, cases of nesidioblastosis have been reported, especially if they are subsidiaries of a gastric bypass with "Y de Roux" reconstruction. The mechanism, for which they could be related, is unknown but, it could be a reactive condition to hormonal pathology and metabolic changes obtained with surgical treatment. Some authors suggest a likely increase in beta-cytotropic factors that produce hypertrophy of the pancreatic beta cells, such as IGF2, IGF1 R α and TGFb R3. There are experimental studies with rodents exposed to incretin analogs used for diabetes, which showed cell proliferation [8–10].

Multiple episodes of hypoglycemia, particularly evening and night and regardless of intake are the main clinical nesidioblastosis. Most patients present the Whipple's triad with adrenergic symptoms (tremor, anxiety, palpitations, and diaphoresis) and neuroglycopenic (amnesia and confusion, loss of consciousness, blurred vision) [1,3,4].

There are major and minor criteria that define nesidioblastosis from histologically. The major criteria are: Exclusion of an insulinoma by macroscopic, microscopic, and immunohistochemical examination, multiple b-cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm, islets with normal spatial distribution of the various cell types and no proliferative activity of endocrine cells; and the minor criteria are: irregular shape and occasional enlargement of islets, increased number of islets, lobulated islet structure and macronucleoli in b-cells. Major criteria were present in each case and are essential for the diagnosis. Minor criteria were present in some but not all cases [11].

In our patient, the pancreatic segment weighed 39 g and measured $6 \times 3.5 \times 2.2$ cm, and presents found that the four major criteria were definitive for diagnosis of disease and irregular shape and occasional enlargement of islets and increased number of islets. Fig. 1 shows pancreatic islets of different shapes and sizes; with