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Original Article

SURGICAL TREATMENT OF PANCREATIC INSULINOMAS

Tratamento cirúrgico dos insulinomas do pâncreas

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ABSTRACT – ***Background*** - Insulinoma is a pancreatic neuroendocrine tumor originated from pancreatic islet beta cells. Although rare, is the most common pancreatic endocrine tumor, with about four cases per million people. The preferential treatment of insulinoma is surgical. ***Aim*** - To analyze the epidemiological, pathological, clinical and surgical patients treated in the last decade in two surgical services. ***Methods*** - Were retrospectively reviewed the medical records of patients undergoing surgical treatment of insulinoma in the period of 1999 to 2011. Demographic data, type and duration of symptoms, associated or not with endocrine syndrome and diagnostic tests were obtained from medical records. Were analyzed the method of surgery, intraoperative findings and immediate and late complications. ***Results*** - Sixteen patients with insulinoma underwent surgical treatment, 68,7% were women. The age ranged from 20 to 60 years, with a mean age of 39 years. Only one case was associated with multiple endocrine neoplasia type 1. Neuropsychiatric manifestations, mainly syncope , were the most prevalent. The average duration of clinical manifestations until the diagnosis was one year and a half. Imaging tests were used in all patients with 68.7% of preoperative tumor localization. All operations were performed in a conventional (open) manner, without use of laparoscopy. The lesions were identified in all portions of the pancreas with the majority in the pancreatic head. Relief of symptoms was not obtained only in one patient. There were no deaths among the patients. ***Conclusion*** - The diagnosis of insulinoma is often established after several months of the onset of clinical manifestations and surgical treatment is curative in almost all patients.

HEADINGS - Insulinoma. Neoplasm. Pancreas.

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RESUMO – ***Racional*** - O insulinoma do pâncreas é neoplasia neuroendócrina proveniente das células beta das ilhotas pancreáticas. Apesar de rara, é a neoplasia endócrina pancreática mais comum, com cerca de quatro casos por milhão de pessoas. O tratamento preferencial dos insulinomas é cirúrgico. ***Objetivo*** - Analisar as características clínicas, epidemiológicas, cirúrgicas e anatomopatológicas dos pacientes tratados na última década em dois serviços. ***Métodos*** - Foram revisados retrospectivamente os prontuários dos pacientes submetidos à cirurgia para tratamento de insulinoma no período de 1999 a 2011. Dados demográficos, tipo e duração dos sintomas, associação ou não à síndrome endócrina e exames diagnósticos foram obtidos dos registros de prontuários. Analisaram-se, também, o método cirúrgico, achados intra-operatórios e complicações imediatas e tardias. ***Resultados*** - Dezesseis pacientes com diagnóstico de insulinoma foram submetidos ao tratamento cirúrgico. Foram excluídos dois por falta de registros completos no prontuário. Do total, 68,7% eram mulheres. A idade variou de 20 a 60 anos, com média de 39 anos. Apenas um caso era associado à síndrome de neoplasia endócrina múltipla tipo 1. Sintomas neuropsiquiátricos, principalmente a síncope, foram os mais comuns. A duração média das manifestações clínicas até o diagnóstico foi de um ano e meio. Exames de imagem foram utilizados em todos os pacientes com 68,7% de localização pré-operatória do tumor. Todas as operações foram realizadas de forma convencional (aberta), sem uso da laparoscopia. As lesões foram identificadas em todas as porções do pâncreas sendo a maioria na cabeça pancreática. O alívio dos sintomas só não foi obtido em um paciente. Não houve óbito entre os pacientes analisados. ***Conclusão*** - O diagnóstico de insulinoma é frequentemente estabelecido após vários meses do início das manifestações clínicas e o tratamento cirúrgico é curativo na quase totalidade dos pacientes.

DESCRITORES - Insulinoma. Neoplasias. Pâncreas.

INTRODUCTION

The insulinoma is a neuroendocrine neoplasm from the pancreatic beta cells in pancreatic islets. It was first described by Nicholls on 1902[7] and by Wilder in 1927[15], but there was better understanding of the disease from the studies of Whipple and Frantz in 1935[14]. Although rare, is the most common pancreatic endocrine tumor, with about four cases per million people[1].

It's landmark is the triad of Whipple, characterized by symptoms of hypoglycemia, low blood glucose (40-50 mg / dL) and relief of symptoms with the intravenous administration of glucose. Although classic, this triad is not on its own diagnostic; may be also caused by administering fictional antihyperglycemic agents and other organic causes of hyperinsulinism. The measurement of serum insulin has proven useful for the diagnosis, and it is important the demonstration of elevated insulin (> 5 microU / mL) during an episode of symptomatic hypoglycemia. The relationship between insulin (microU / ml) and glucose (mg / dL)> 0.4 is highly suggestive, as well as increased levels of C-peptide (> 2 nmol / L)[3,8]. Increased levels of C-peptide are also valuable diagnostic, excluding the possibility of fictional disease.

Most insulinomas are benign (only 5-10% malignancy), almost always unique (only 10% multiples, and these are usually associated with the multiple endocrine neoplasia type 1 syndrome MEN 1), small and have a uniform distribution on the pancreatic parenchyma[2,3].

The preferred treatment is surgery, performed in a conventional or laparoscopic manner, and with or without additional method for intraoperative location of the lesion[1,9,11].

The present study aims to analyze the clinical, epidemiological, pathological and surgical patients treated in the last decade in two surgical services.

METHODS

Were retrospectively reviewed the medical records of patients undergoing surgical treatment of insulinoma in the services of Digestive Surgery from Hospital de Clínicas of Universidade Federal do Paraná and Hospital Nossa Senhora das Graças, in Curitiba, Paraná, Brazil in the period 1999 to 2011. Two patients were excluded for lack of complete records on the chart.

Demographic data, type and duration of symptoms, association or not with endocrine syndrome and diagnostic tests were obtained from registries of medical records. It was also analyzed, the surgical approach, intraoperative findings and complications.

It was considered the quality of resection based on the R rating, the International Union Against Cancer - UICC (Rx = presence of residual tumor could not be evaluated; R0 = no residual disease, microscopic residual disease = R1 and R2 = macroscopic residual disease)[12]. Characteristics of the surgical specimens in relation to size, histology and invasion were reviewed. Finally, the postoperative complications were revised immediate and long term, as the resolution of symptoms.

RESULTS

Sixteen patients with insulinoma underwent surgical treatment.

Table 1 shows the demographic characteristics of the studied population. Eleven patients were women (68.7%) and mean age was 39 years. The body mass index (BMI) ranged from 22.3 to 44.1. Only one patient was brown, the rest Caucasian. Only one case was associated with the multiple endocrine neoplasia syndrome 1 (MEN1). No patient had a family history of insulinomas. In relation to lifestyle and comorbidities, 12% of patients were smokers and 25% consumed alcohol. As associated diseases, was observed two cases of hypertension, a polycystic kidney, one hypothyroidism, a rheumatic fever and a severe atopic dermatitis.

TABLE 1 – Demographic data of patients with insulinoma (n = 16)

Sex (fem/masc in %)	68,7/35,5
Age	39,6 (20-60)
BMI	26,4 (22,3-44,1)
Race (white in %)	93,7

The clinical manifestations are shown in Table 2, with mean duration of about one year and a half (19.5 months), but with three cases of four years duration. Neuropsychiatric manifestations was prevalent. The most common symptom was syncope occurring in more than 40% of the patients. There was extreme symptoms, such as a patient who was oligosymptomatic, and other, which had its diagnosis after hypoglycemic coma. No patient had weight loss, five had no change and the rest had significant weight gain, with an average of 8.6 kg. All patients obtained immediate relief of his symptoms with glucose administration.

The diagnostic methods were laboratory and imaging. The fasting glycemia was evidenced below 50 mg / dL in all patients. There was a range from 18 to 46 mg / dL, with an average of 35 mg / dL. The fasting test was performed in 93.7% of patients with positive results in all of them. The measurement of fasting serum insulin was performed in all patients

and the insulin / glucose was obtained with values above 0.4 in 75% of them. The C-peptide was measured in 10 patients, with its maximum at 4.9 nmol / L. In some patients, laboratory investigation included measurements of other hormones to exclude other causes of hypoglycemia.

TABLE 2 – Clinical manifestations of patients with insulinoma (n= 16)

Duration (months)	19,5 (3-48)
Syncope (%)	43,7%
Seizures (%)	37,5%
Vertigo (%)	37,5%
Confusion (%)	31,2%
Sweating (%)	31,2%
Tremors (%)	18,7%
Exacerbation with exercise (%)	31,2%
Weight gain (kg)	8,68 (2-20)

Imaging tests were used in all patients with 68.7% of pre-operative localization of the tumor. Ultrasonography was performed in nine patients and could detect any lesion (eg, hypoechoic mass) only in three patients. Computed tomography was successful in detecting the lesion in four of the 16 patients in which were performed (25%). All lesions detected by CT were over 1.5 cm (the largest with 11 cm). Thirteen patients required a second imaging method, five of a third and four of a fourth method for correct identification of the lesion. Eight MRIs performed and only two were positive for identification of the tumor (25%). The endoscopic ultrasound was used in four patients preoperatively with success in the location of the lesion in all of them. Selective arteriography of the celiac trunk was used in one patient without success in locating the lesion.

All operations were performed in a conventional manner without use of laparoscopy. Were performed seven simple enucleations, five distal pancreatectomy, two subtotals pancreatectomy, two pancreas body and tail removal associated with enucleation (one of which was also associated with the removal of the parathyroid glands in the same surgery - a patient with MEN1). In five cases there was an association of splenectomy (all procedures performed before 2005, distal pancreatectomy associated or not with enucleation with splenic involvement seen in two cases). The surgical time ranged from 150 minutes to six hours. In one case the lesion was not palpable by the surgeon. Intraoperative ultrasonography was used as an auxiliary to palpation in 14 cases, with positive location of the lesion in all of them. Figure 1 shows the images of the process of identifying a lesion by intraoperative ultrasound, monitoring of vascularization and the relationship with the pancreatic duct in one patient in the series. The test was not performed in a case where the lesion was 12 cm and involved the spleen and in another case of a lesion of 2 cm in the pancreatic head.

The lesions were identified in all portions of the pancreas the majority 31%, in pancreatic head. There were fragment sent to intraoperative frozen section biopsy in 11 cases, with six reports

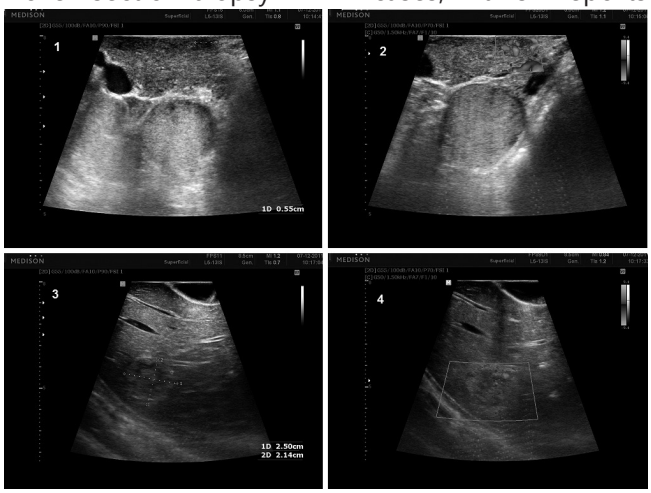

FIGURE 1- Intraoperative localization of the lesion with the use of ultrasound associated palpation, numbered according to the sequence of images acquired with analysis of the lesion, the vascularization and relation to the pancreatic duct

suggestive of endocrine neoplasia, four of neoplasia of probable benign behavior and one suggestive of adenocarcinoma. All patients had their blood glucose monitored intra-operatively and there was no immediate complication in any case.

Relief of symptoms was not obtained in only one patient. All had hyperglycemia in the first post-operative, except the patient who received no improvement of symptoms. The average hospital stay was 18 days.

Seven patients developed pancreatic fistula, four had wound infection and four had intra-abdominal collections. One patient had atrial fibrillation with instability on the 5th day after surgery and had to had cardiac defibrillation. There was a case of pancreatic pseudocyst of 20 mm diagnosed five months after surgery. One patient developed incisional hernia and diabetes later. There were no deaths among patients.

In the analysis of the surgical species, the dimensions of the lesions ranged from 0.68 cm to 12 cm, with the vast majority with dimensions around 1.5 cm in its longest axis. The location was in the entire pancreatic length with five findings in the head, three in the body, three at the transition body to tail, three in the tail and two in uncinate process. The most prevalent histological diagnosis was well differentiated neuroendocrine tumor of uncertain behavior. Only one case revealed invasive tumor at the analysis (lesion of 12 cm, with splenic involvement). The margins were R0 in nine patients, R1 in two and not reported in other cases.

Lymphnodes were free of disease in all cases, except that there was already documented invasion.

DISCUSSION

Due to low incidence of insulinoma, most of the studies is about few cases or multi-institutional. Recommendations on the preoperative investigation, better surgical techniques and prognostic factors are still reason of discussion. Of the neuroendocrine tumors of pancreas insulinoma is the most common, representing 70% of them [1,3,8].

In this series, were more prevalent in females (68%), in accordance with the data of large studies[1,6,8]. The patients' ages stood around 40 years, with 81% of patients aged less than 50 years. Most patients with this tumor were between 30 and 60, although there are reports of disease occurrence in the extremes of age[1,4].

Diagnosis can be difficult in some cases due to the predominance of neuropsychiatric symptoms that have multiple differential diagnoses. The longest delay was four years, averaging one and a half to obtain the diagnosis.

Since the hospitals involved had residency program, patients were extensively investigated by laboratory tests, being especially important the determination of C-peptide to exclude factitious illness in some cases. The test of hypoglycemia with fasting is widely accepted to obtaining a diagnosis with great positiveness, as demonstrated in the present series[5,11].

After confirmed the diagnosis, the challenge is the tumor location, since in the great majority they are small tumors, as well as in this present study, which largely had less than 1.5 cm at its greatest diameter[9,10].

There are several methods of imaging available, being necessary usually more than one for location of the lesion. CT scan showed positivity in 25%, similar to other series, but below the sensitivity of 63% described for helicoidal CT[5,13]. Ultrasonography revealed positivity in 33%, well above described, which can be explained by the size and location of the three lesions that were found by ultrasound in this series. The most accurate preoperative examination was endoscopic ultrasound, which showed 100% positivity. In 31% of cases the patients were taken to surgery without preoperative localization of the tumor. In these, there was resolution of the problem with intraoperative ultrasonography associated with palpation method previously described as highly sensitive in the literature and been successful in 100% of cases in this study.

In this sample, the tumor was slightly more prevalent in the pancreatic head, and the literature shows equal distribution in the pancreatic parenchyma[2,3,9]. There were no deaths. The post-operative morbidity was 43.7%, being the main cause pancreatic fistula. Of these, however, there was spontaneous resolution in all cases, with the longest hospital stay of 40 days. Almost all patients had immediate solving of their symptoms, presenting hyperglycemia within the first days post-operatively, except in one patient. In this case the lesion was identified intra-operatively and enucleated, but she persisted with lower levels of blood glucose within days of operation, better than the previous, but still low. Discharged with octreotide with satisfactory control of symptoms in an outpatient setting.

CONCLUSION

The diagnosis of insulinoma is often established after several months of the onset of clinical manifestations and surgical treatment is curative in almost all the patients.

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