SURGICAL TREATMENT OF HYPERINSULINISM DURING THE COURSE OF PANCREATIC CANCER (INSULINOMA) – ONE CENTER EXPERIENCE

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Endogenic hyperinsulinism is mainly caused by neuroendocrine tumors (insulinomas) which autonomously secrete insulin. Because the symptoms are often aspecific, a considerably delay in diagnosis occurs. The treatment consists of operative removal of the tumor from the pancreas, preceded by pre-operative localization. In this article we describe our experience with surgical removal of insulinomas

Material and methods. We retrospectively analyzed all patients with insulinoma which were treated in our center. Definitive diagnosis was made using a 72-hours glucose fasting test. We describe the symptoms, localization techniques and the outcomes after surgery.

Results. Between January 2002 and May 2011, 45 patients (35.6% men and 64.4% female) were treated in our center. The most prevalent symptoms were altered consciousness and general malaise. The combination of CT-scan and endoscopic ultrasound had the highest (90%) sensitivity to localize tumors pre-operatively. During surgery, in 40 patients (89%) the tumor could be removed by enucleation. In the other five patients partial pancreas resection was required. In 22 patients (49%) we used intra-operative insulin level measurements to confirm complete tumor resection. Within the first month after surgery, two patients (4.4%) developed acute pancreatitis, four patients (8.8%) developed a pancreatic fistula. One patient died of multi-organ-failure. All patients were free from symptoms of hyperinsulinism after the surgery and after a median follow-up of 4.5 years.

Conclusions. Based on the experience with 45 patients, surgical removal, aided by pre-operative localization with CT and endoscopic ultrasonography, is an effective and safe treatment for insulinomas.

Key words: hyperinsulinism, insulinoma, pancreas, surgical treatment

Insulinoma is a tumor derived from pancreatic beta type cells, belonging to the group of pancreatic neuroendocrine cells. The frequency of occurrence of the above-mentioned is 1-4 cases per one million inhabitants (1, 3). The mean patient age of insulinoma diagnosis is 50 years. Patients with polyglandular endocrine adenomatosis (MEN1) are an exception with diagnosis established in younger patients. In most cases (90%) the tumors are benign, isolated, and small in size (diameter < 2 cm). Only in 10% of patients the tumor is malignant with metastases to the liver and surrounding lymph nodes (1).

Hyperinsulinism symptoms during the course of insulin-secreting insulinoma are inconclusive and one may only be suspected of the above-mentioned pathology.

The tumor is responsible for the hypersecretion of insulin. Most common symptoms are associated with neuroglycopenia, including syncope, seizures, and vision, concentration, and speech disturbances. Other symptoms are associated with autonomous nervous system disturbances, including heart palpitations, excessive sweeting, and vomiting. Additionally, patients with organic hyperinsulinism during the course of pancreatic insulinoma might present with weight disturbances. Most often such patients gain weight associated with excessive food consumption, as a prevention or reduction of hypoglycemia (2).
Uncharacteristic symptoms are responsible for erroneous diagnosis, and patients are often treated for epilepsy, ischemic heart disease, anxiety, peptic ulcer disease and other pathological conditions. The time from onset of symptoms to diagnosis of organic hyperinsulinism is different and varies between two months and several years.

The diagnosis of organic hyperinsulinism is based on biochemical parameters performed during a 72-hour fasting test (3). The patient receives oral fluids devoid of glucose and intravenous physiological saline. The following parameters are estimated: glucose, insulin and peptide C levels at specified time intervals. Throughout the duration of the test the patient is under observation, in order to capture symptoms of hypoglycemia, which terminates the test. It is important to assess the glucose and insulin levels. In most patients (99%) with organic hyperinsulinism the fasting test ends within the 72-hours (4). Hyperinsulinemia is diagnosed when the insulin level exceeds 36 pmol/l, the glucose level is below 2.3 – 2.5 mmol/l, and the insulin/glucose ratio is greater than 0.3. Additionally, the peptide C level should exceed 200 pmol/l, and tests for sulphonyl urea derivatives prove negative.

Before surgical treatment, one should, if possible, localize the lesion responsible for hyperinsulinism. This enables to plan surgery and reduce the number of complications. Insulinomas are usually small in size tumors often difficult to distinguish from normal pancreatic parenchyma. Unfortunately, this complicates preoperative diagnostics. Currently, considering insulin-secreting insulinomas computer tomography seems to be the most important method. The sensitivity of the examination amounts to 90% (5). The use of intravenous contrast enables to detect well-vascularized tumors, such as insulinomas (6).

Endoscopic ultrasonography (EUS) is becoming more and more important. The sensitivity of the examination ranges between 80-90% (7). Thanks to the high resolution of the above-mentioned it is possible to localize even small lesions, in order to assess the relationship of the tumor to the pancreatic duct and vessels (splenic artery and portal vein) (7).

The combination of both computer tomography and endoscopic ultrasonography allows too increase the sensitivity too as much as 100% (8). The remaining available diagnostic methods are less important because of their lower sensitivity.

Intraoperative ultrasonography is also an important method used when localizing tumors. Similarly to EUS, its high resolution enables to detect small lesions. It is also useful to confirm the presence of tumors with an uncertain preoperative location.

The only effective method of treating patients with hyperinsulinism is the surgical excision of the lesion. The percentage of recovery is estimated at 77-100% (9, 10).

In 1927, dr William J. Mayo was the first to perform such an operation. The tumor proved to be malignant. The patient died one month after the operation (11).

MATERIAL AND METHODS

During the period between 2002 and 2010, 45 patients with organic hyperinsulinism during the course of insulin-secreting insulinomas were treated at the Department of General, Vascular and Transplant Surgery, Medical University of Warsaw. The study group comprised 64.4% female and 35.6% of male patients. Mean age amounted to 48 years.

Diagnosis of hyperinsulinism was based on biochemical examinations. All patients were subject to the 72-hour fasting test, during which glucose, insulin and peptide C levels were determined. Two patients underwent previous tail and body and tail pancreatic resections. The histopathological examination in both cases confirmed the presence of an insulinoma. However, due to persistent symptoms of hyperinsulinism re-diagnosis was performed, confirming the presence of yet another lesion responsible for hyperinsulinism.

In case of two patients hyperinsulinism was diagnosed during the course of polyglanudlar endocrine adenomatosis (MEN1).

Table 1 presented hyperinsulinism symptoms.

The average time from onset of hyperinsulinism symptoms to diagnosis was 29 months (maximum – 193 months, minimum – 3 months).

Most of the patients shared the occurrence of hypoglycemia and its symptoms with exercise. Symptoms were more intensified during fasting, before breakfast. Additional meals and sweet drinks allowed to prevent hypoglycemia. Many patients ate several times a day. Only five pa-
patients significantly gained weight during the course of the disease (an average of 10 kg).

The following examinations were performed, in order to localize the tumor: abdominal ultrasonography (US), endoscopic ultrasonography (EUS), computer tomography (CT), magnetic resonance (NMR), intra-arterial stimulation of pancreatic segments by means of calcium ions (ASVS), somatostatin receptor scintigraphy (tab. 2).

The transverse incision was most often performed. Abdominal cavity organs were evaluated, especially the liver, in search of metastatic lesions. Afterwards the pancreas was subject to palpation. The opening of the omental sac and separation of the omentum from the transverse colon, and Kocher’s maneuver enabled to determine the head and body of the pancreas. The splenic curvature was prepared in patients preoperatively suspected of a pancreatic tail tumor.

The tumor was removed with a small margin of healthy tissue. In order to reduce the risk of postoperative pancreatic fistula development, during the surgical removal of the tumor, electrocoagulation and non-absorbable polypropylene sutures were used. Additionally, after the removal of the lesion the operative field was closed by means of non-absorbable sutures. At the site of the enucleation a latex drain was left intact. The peritoneal and abdominal cavities were closed by means of layered sutures.

In each case, the location of the tumor was confirmed by means of intraoperative palpation. In case of ten patients with doubtful preoperative tumor localization, intraoperative ultrasonography was performed.

Intraoperative insulin level estimation was performed in 22 patients, in order to determine the radicalism of the procedure. The chemiomunoluminescence method was used. 4ml of blood was collected into a tube with an anticoagulant (versenate/EDTA). Results were obtained within 8-10 minutes, since blood collection. The insulin level was expressed in pico-moles/liter (pmol/L).

The first measurement was performed at the beginning of the operation from peripheral and venous blood. When the pancreas was visualized portal venous blood was collected, before palpation. After collecting blood the puncture site was compressed for a period of 1-2 minutes. Ten minutes after the removal of the tumor yet another blood sample was collected from the portal vein.

The final measurement was performed at the time of the abdominal wall closure. Blood was collected from the peripheral vein.

A decrease in the insulin level by 20-30% after the removal of the tumor was evidence of the radical excision of the lesion.

RESULTS

Table 3 presented the sensitivity of preoperative examinations.

Intraoperative ultrasonography enabled to localize the lesions in 7 patients. The intraoperative insulin measurement in 3 of 22 patients proved abnormal (not fulfilling measurement

<table>
<thead>
<tr>
<th>Type of examination</th>
<th>No of patients</th>
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<tbody>
<tr>
<td>US</td>
<td>25</td>
</tr>
<tr>
<td>EUS</td>
<td>30</td>
</tr>
<tr>
<td>TK / CT</td>
<td>39</td>
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<tr>
<td>NMR</td>
<td>5</td>
</tr>
<tr>
<td>ASVS</td>
<td>6</td>
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<td>Scintigraphy</td>
<td>2</td>
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Table 3. Sensitivity of preoperative examinations

<table>
<thead>
<tr>
<th>Examination</th>
<th>Sensitivity %</th>
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<tbody>
<tr>
<td>US</td>
<td>9</td>
</tr>
<tr>
<td>TK / CT</td>
<td>68,4</td>
</tr>
<tr>
<td>EUS</td>
<td>80</td>
</tr>
<tr>
<td>NMR</td>
<td>66,6</td>
</tr>
<tr>
<td>TK + EUS / CT + EUS</td>
<td>90</td>
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criteria, both in peripheral and portal blood). In case of one patient subject to “blind pancreatic tail resection” the intraoperative measurement of insulin proved to be the only method that confirmed the radical excision of the tumor responsible for hyperinsulinism. There were no complications associated with portal vein puncture.

Figure 1 presented the localization of the lesions.

In case of 41 patients the tumor was subject to enucleation from the surrounding pancreatic parenchyma.

The resection of the tail of the pancreas was performed in four patients, while the resection of both the body and tail of the pancreas in one. In case of two patients this was associated with the inability to enucleate the tumor, which was located deep in the pancreatic parenchyma. In case of another patient the enucleated tumor was macroscopically heterogenous, while the histopathological examination showed that there were at least two lesions. Thus, the patient was subject to pancreatic tail resection. In one case, after the enucleation of the tumor the palpation method revealed the presence of three additional lesions located in the tail of the pancreas, which were eventually resected. The patient underwent resection of the body and tail of the pancreas. In one patient we failed to localize the tumor before the operation, as well as intraoperatively. Therefore, the patient underwent resection of the body and tail of the pancreas. The histopathological examination of the removed pancreas revealed the presence of three lesions.

All patients presented with symptoms of organic hyperinsulinism. Hypoglycemia was not observed during the postoperative period. Most patients presented with hyperglycemia, which lasted 2-3 days and did not exceed 300 mg/dL. Exogenous insulin was not administered.

The histopathological evaluation of the intraoperative material (45 patients) confirmed the diagnosis of a well-differentiated neuroendocrine tumor with a positive reaction towards staining for insulin, chromogranin, and synaptophysin.

Surgical complications

Splenectomy was performed in five patients, including three during the resection of the tail of the pancreas, due to anatomical conditions. In case of two patients splenectomy was performed because of iatrogenic reasons.

Acute pancreatitis during the postoperative period was observed in two patients. These patients were subject to conservative treatment. Full recovery was observed.

Pancreatic fistula development was observed in case of elevated amylase levels collected from the drian left in the operative field. The above-mentioned was observed in four patients, including two with acute pancreatitis. One patient died during the postoperative period, due to multiorgan failure during the course of acute pancreatitis.

RESULTS

In order to determine distant results the operated patients were contacted. They either received a questionnaire by mail or a phone call. Questionnaire responses were received.
from 39 patients or their family members. One patient died three years after the operation, due to lung cancer and cerebral metastases. One patient was diagnosed with recurrence of type 2 diabetes mellitus; symptoms disappeared two years before the onset of the insulinoma. After surgery the patient returned to oral hypoglycemic drugs. The remaining patients denied the recurrence of hypoglycemic symptoms.

**DISCUSSION**

An isolated insulin-secreting insulinoma is the most common cause of organic hyperinsulinism (1). The study group comprised 42 such patients. The remaining three patients were diagnosed with multiple tumors during histopathological evaluation.

Due to the small size of the tumors, preoperative localization seems important. All patients operated in our department were subject to thorough preoperative diagnostics. Best results were obtained after CT and EUS. Considering our material the sensitivity of the above-mentioned methods amounted to 90%. This is in accordance with literature data (8). The remaining methods seem less important. However, one should not forget about these methods using them in case of difficulties with the localization of the tumor. Preoperative tumor localization enables safe preparation in the pancreatic parenchyma. This reduces the risk of surgical complications, such as pancreatic fistulas.

Based on our own experience we believe that careful pancreatic palpation during surgery is essential. Some Authors’ consider pancreatic palpation as the essential method in the diagnosis of insulin-secreting insulinomas (12).

Intraoperative ultrasonography is also helpful enabling to confirm the existence of a lesion, and assess its position in relationship to the pancreatic duct and vessels. In combination with intraoperative pancreatic palpation the above-mentioned increases the possibility of finding the lesion or confirmation of the preoperative localization (13, 17).

The intraoperative insulin level measurement is a valuable tool when evaluating the radicalism of tumor excision (14). In case of one of our patients, in whom the localization of the lesion responsible for hyperinsulinism was not possible (the patient was subject to distal pancreatic resection), the insulin level after the resection significantly decreased. The histopathological examination confirmed the presence of an insulinoma.

The most common surgical procedure consists in the enucleation of the tumor. This is possible because of the good demarcation of the lesion from the normal pancreatic parenchyma. The resection of the tail or body and tail of the pancreas is necessary in patients in whom the localization of the tumor proved impossible, and hyperinsulinism symptoms are severe, threatening the patients’ life (15, 17).

Postoperative hyperglycemia is an interesting phenomenon, which probably is a response of the organism to the removal of the insulin-secreting tumor, inhibiting the regulation of insulin secretion. In such cases one should refrain from the administration of exogenous insulin, in order to restore proper carbohydrate balance. The above-mentioned is additional evidence of the radicalism of tumor excision responsible for hyperinsulinism (16).

Treatment of patients with organic hyperinsulinism requires a multidisciplinary approach. Surgical management is currently the only effective method. The exact preoperative localization of the tumor, important intraoperative examination by means of palpation, and appropriate choice of the surgical procedure allow for complete recovery of the patient.

**REFERENCES**


Received: 4.12.2012 r.
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