The insulinoma as a diagnostically and therapeutically challenging neoplasm

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Abstract:

Introduction and purpose

    An insulinoma is the most common neuroendocrine tumor of a pancreas. This tumor produces insulin, which in excess causes hypoglycemic attacks, provoked by hunger or physical effort. Delays in diagnostic processes of the insulinoma are associated with the misattribution of symptoms to cardiac, psychiatric or neurological disorders. Thus, the suitable diagnostic procedures play a significant role as they ensure quick introduction of treatment. The purpose of this work is to evaluate advances in demanding diagnostically and therapeutically insulinoma.

A brief description of the state of knowledge

    The used method was a literature review. The basic and the most common method of treating the insulinoma is a surgery. Due to this, finding precise location of the tumor preoperatively is crucial. In the diagnostics of the insulinoma both basic CT and MRI contrast enhanced and an endoscopic ultrasound, a selective arterial calcium stimulation test and the latest molecular imaging are used. In treatment process not only traditional surgical excisions were performed, but also laparoscopic and robotic surgeries turned out to be success.

Conclusions

    Summing up, the insulinoma is a neoplasm with a wide range of therapeutic and diagnostic solutions, thanks to the progress that has been made in recent years. Although there are many difficulties on a diagnostic path of the insulinoma, new solutions and appropriate aproach make this process easier. Nevertheless, doctor's diagnostic vigilance is essential, because consideration in the differential diagnosis the insulinoma is an essential step and without this step any further actions can be taken.

Key words: Neuroendocrine pancreatic tumor; diagnosis, molecular imaging; treatment; robotic surgery

Introduction and purpose

    Insulinomas are derived from pancreatic β-cells and they are the most common cause of hypoglycemia related to endogenous hyperinsulinism with an incidence of 4 per 1 million people of the general population. However, the incidence is likely to be underestimated due to the small size of insulinomas [1]. Insulinomas are neuroendocrine tumors (NETs), which were previously considered rare, but now they are becoming more common in most countries and are gaining popularity [2]. They are occurring mostly between the ages of 41 and 50 [3]. Most of the insulinomas (90%) have been reported to be benign. They can occur sporadically or be associated with the multiple endocrine neoplasia type 1 (MEN-1) [4]. This syndrome is characterized by primary hyperparathyroidism, anterior pituitary adenomas, and tumors of the endocrine pancreas and duodenum. Unlike sporadic insulinomas, which usually present as single, benign encysted lesions, MEN-1 associated insulinomas develop earlier and tend to be multifocal, spreading throughout the pancreas [5].

    The first diagnostic steps of insulinoma constitute symptoms which are related to overproduction of insulin by tumor and consequently to a hypoglycemia. Neuroglycopenic symptoms vary in spectrum and include weakness, confusion, behavioral changes, personality changes, visual disturbances, seizures, loss of consciousness, coma or amnesia.

Moreover, hypoglycemia causes catecholamine release and adrenergic sympathetic nervous system activation, what is responsible for symptoms such as: sweating, anxiety, palpitations, tremors and overweight or obesity. Whipple observed that symptoms are arranged in characteristic triad called „Whipple's triad" which contain of: hypoglycemia (glucose level below 50 mgs/dl), neuroglycopenic symptoms, fast relief of symptoms after glucose intake. [1] The presence of this triad is considered to be useful in establishing diagnosis.[3]

However, diagnosis of the insulinoma can be difficult and demanding. The symptoms are not unique only to hypoglycemia, but they can be associated with cardiac, psychiatric or neurological disorders [4]. Differential diagnosis of the insulinoma includes many disease entities such as an intoxication, an epilepsy, the Addison's disease, a generalized liver disease. Putting patient's on weight, which is connected with strong hunger caused by hypoglycemia, resulting in excessive caloric intake and discourages from considering a neoplastic lesion [6]. Although it was considered that symptoms of the insulinoma appear in the fasting state or after physicals exercise, it is now proved that postprandial symptoms are as well observed [1]. Thus, diagnostic vigilance should be preserved as well as progress in this process should be achieved to prevent delay in diagnosis and allow to perform a surgery, which is the most often method of treatment. It is observed that recently have been many advances, well described in reviews on imaging NETs [2]. The purpose of this work is to evaluate advances in diagnostic and treatment of insulinoma. For this purpose a literature review was performed.

Description of the state of knowledge about diagnostic

The 72-h monitored fasting test (together with measurement of the levels of plasma glucose, insulin, C-peptide and proinsulin) remains the gold standard for diagnosis of an insulin-secreting tumor. After biochemical confirmation of insulinoma, medical imaging is recommended. An intraoperative ultrasound has a very high positive detection rate, however revealing the insulinoma before a surgery treatment makes surgery easier [3,7]. The small size of insulinomas challenges the detectability by conventional imaging techniques like contrast-enhanced CT and contrast enhanced MRI beacause of motion artifacts. On the other hand, an endoscopic ultrasound is invasive technique and the visualisation of pancreas is not always possible. It has a positive rate of 80–89%, depending on the operator's technique and experience [7]. The selective arterial calcium stimulation test with hepatic venous sampling (SACST) is used when the preoperative localization of insulinomas by previous techniques is not possible. In this test calcium gluconate is injected into the gastroduodenal, splenic, and superior mesenteric arteries with subsequent sampling of the hepatic venous effluent for insulin. Calcium stimulates the release of insulin from hyperfunctional β cells in the insulinomas but not from healthy β cells. Thanks to this, surgeon can limit the intraoperative search of the insulinoma to the corresponding arterial territory. Based on the systematic review and metaanalysis it has a significant importance in localization of insulinoma [7]. However, SACST determines only the arterial territory and not the tumor itself and is invasive procedure [8].

A solution is new non-invasive technique – molecular imaging which has the potential to replace the invasive localization of insulinomas. Receptors for the incretin glucagon-like peptide-1 (GLP-1R) have been found overexpressed in nearly 100% benign insulinomas with an about 5 times higher density of GLP-1R on insulinomas compared to normal β cells.

Targeting GLP-1R with indium-111, technetium-99m or gallium-68-labeled exendin-4 offers a new approach that provides the successful localization of small benign insulinomas preoperatively. Based on the pilot study, it is prooved that gallium-68-labeled exendin-4 is sensitive in a correct preoperative detection of the hidden insulinomas. It had already detected the insulinoma by 2,5 hours after injection. Gallium-68-labeled exendin-4 PET/CT revealed higher tumor to background ratios than indium-111-labeled exendin-4 SPECT/CT because of an advantageous partial volume effect in PET and faster blood clearance of Gallium-68-labeled exendin-4 [9,10]. Authors of a prospective cohort study conclude that Gallium-68-labeled exendin-4 PET/CT is highlier sensitive for the detection of insulinomas than CT, MR and endoscopic ultrasonography [11]. Malignant insulinomas express more frequently the somatostatin subtype 2 receptors (SSTR2). The challenge in metastasizing insulinomas is to define the extension of disease and offer a targeted therapy. The molecular imaging can deal with this problem [8].

Insulinoma-associated protein 1 (INSM1) is a promising, potential biomarker and therapeutic target for neuroendocrine tumors. Expression of INSM1 has been observed among others in insulinomas. The expression of INSM1 in pancreatic tumors has been reported very recently and it helps in determining whether a particular pancreatic neuroendocrine tumor is a focal insulinoma or a metastatic pancreatic neuroendocrine tumor. In addition, expression of INSM1 has been used as a modern biomarker for the diagnosis of pancreatic neuroendocrine tumor like the insulinoma [12].

Description of the state of knowledge about treatment

Most benign, sporadic insulinomas are treated successfully by complete surgical excision. At surgical exploration, the entire abdomen is inspected for evidence of metastatic disease or extrapancreatic tumors that secrete insulinoma-related growth factors. Next, the entire pancreas is exposed to palpate any tumors. Palpation of the pancreas effectively localizes the insulinoma 70% of the time. Next, intraoperative ultrasound, which has an 86% rate of detection, is performed. It is important to remove the tumor with the capsule completely to prevent a local recurrence [5].

The systematic review and metaanalysis, which examined safety of laparoscopic approach for insulinomas, proved that laparoscopic treatment for insulinomas is a safe and feasible approach associated with reduction in length of hospital stay and comparable rates of postoperative complications in comparison to open surgery [13].

The next step forward is robotic surgery. The Robotic surgery systems have been developed to overcome the limitations of laparoscopic surgery. The advantages of robotic surgery include three-dimensional operative view, unrestricted instrument motion, no involuntary tremors. What is more, robotic surgeries show decreased postoperative morbidity and hospital stay and faster recovery of patients compared to the open approaches. The only limitation are the high costs of such device. The first experience about robotic surgery as a treatment of the insulinoma was the 65-years old patient who underwent a robot-assisted pancreaticoduodenectomy (laparoscopic resection and robotic reconstruction) using robot called Revo-i. The operation was successful. The patient's recovery was uneventful, except for mild fever and the patient was discharged on postoperative day 7 [14].

As well as operation, the lifestyle modification is very important. Patients with insulinoma need to avoid driving and excessive excercises. In case of frequent hypoglycemia, patients with insulinoma should supply regularly carbohydrates with a high glycemic index and also prevent long breaks between meals, especially during night breaks [6]. In mild hypoglycemia patient should receive 15 to 20 grams of glucose or fast-acting carbohydrate meal/drink every 15 minutes until restoration of euglycemia, subsequently should ingest a meal rich in complex carbohydrates. In severe hypoglycemia patient should receive 25 gram boluses of 50% glucose every 15 minutes until restoration of euglycemia. In the event of lack of intravenous access or if patients are not able to ingest carbohydrates, intramuscular injection of 1 mg glucagon is recommended. Presently a lot of emphasis is placed on patients and their relatives' education about recognition and reaction to hypoglycemic symptoms [3].

The inhibitory effect of the somatostatin analogue octreotide on the secretion of insulin could be also used in the treatment of insulinoma. In the study group plasma insulin concentrations decreased significantly, but plasma glucose concentrations increased. It means that further studies on the effectiveness of octreotide are needed [15]. However, there is a case of woman with insulinoma, who had been successfully treated with oral diazoxide since 27 years. This therapy was effective and save for her, with only little negative effects. The patient's quality of life obtained from the long term use of diazoxide is sufficiently good that he has chosen to continue medical management rather than require insulin and pancreatic enzyme support after likely total pancreatectomy. Despite medical advances, there will remain patients who are not suitable surgical candidates, among other because of problems with localization the tumor. [16] Moreover, the octreotide can be used in an octreotide test for the prediction of somatostatin receptor (SSTR) 2 expression in insulinomas. Although five SSTR subtypes have been identified in insulinoma cells, octreotide binds with high affinity to SSTR2 and SSTR5. The octreotide test has been reported to be useful for predicting the efficacy of treatment in patients with benign insulinomas [17].

Conclusions

Taking all these factors into consideration, the approach to diagnostic and therapeutic proces of insulinoma has developed in recent years. Many modern diagnostic methods have been introduced and tested. These successes have brought many benefits both to patients and doctors. Doctors have more possibilities of treatment and diagnosis and this solutions make their work easier. On the other hand, patients with insulinoma are more likely to recover and improve their quality and life expectancy. Molecular imaging stands out in particular as it allows to detect insulinoma non-invasively and effectively in comparison to other methods. Operational methods are also at a higher and higher level, including even robotic surgery. Nevertheless, doctors play a crucial role because they have to considerate the insulinoma in the differential diagnosis step and without this step any further actions can be taken.

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