MODERN VIEWS ON TREATMENT OF INSULINOMA

Salimova Dildora Erkinovna
Scientific adviser: Assistant of the Department of Endocrinology, Samarkand State Medical University
Umurzoqov Xurshid
Ismoilov Farrux
Xoshimov Behruz
Mamashukurova Munisa
Students of the Samarkand state Medical University

Annotation: *Insulinoma is the most common hormonally active neuroendocrine tumor (NET) of the pancreas. In recent years, there has been a tendency towards an increase in the incidence of NETs, in particular insulinoma. Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms derived from neuroendocrine cells of the embryonic intestine that have biologically active properties. The most common location of NETs is in the gastrointestinal tract (66%) [1]. NETs are rare types of tumors and are not always accompanied by the occurrence of clinical symptoms, as a result of which information about their epidemiology is very limited.*

Keywords: *insulinoma; surgery; drug treatment; targeted therapy.*

INTRODUCTION

According to the US National Cancer Institute, in 2020 the rate of newly diagnosed neuroendocrine neoplasia was 5.25 per 100,000 population, a marked increase compared to 1973 (1 per 100,000 population), and the prevalence of neuroendocrine neoplasia was 35 per 100,000 population [2]. Functionally active NETs are of particular interest, since overproduction of hormones can lead to severe symptoms that significantly worsen the patient's condition. Insulinoma is the most common NET of the pancreas (P) [3]. According to the epidemiological study, among 229 patients with pancreatic NETs, 48 patients with functionally active NETs were identified, among whom the proportion of patients with insulinoma was 56.3%, with gastrinoma - 25%, with glucagonoma - 4.2%, with other NETs - 14 .9% [4]. Insulinoma is a type of functional NET characterized by hypoglycemia caused by inappropriately high insulin secretion. The incidence of insulinoma is 1–4 cases per million people per year [5]. Most often, insulinoma is a single benign tumor, but in 5.8% of cases, insulinoma is malignant, and in 6–7.6% it is associated with multiple endocrine neoplasia syndrome type 1 (MEN-1) [6, 7]. The main clinical symptom of insulinoma is fasting hypoglycemia, which occurs in 73% of patients. About 20% of patients report symptoms of hypoglycemia both on an empty stomach and after meals. Moreover, in recent years, a trend has been identified towards an increase in the number of patients whose only complaint is postprandial hypoglycemia. Most patients

experience weight gain [7]. Manifestations of hypoglycemia are variable. They may include: feeling of hunger, symptoms of activation of the sympathoadrenal system, incl. palpitations, trembling, sweating, panic attacks, as well as neuroglycopenic symptoms such as blurred vision, confusion, seizures, behavioral changes, amnesia of a hypoglycemic episode [8]. The set of symptoms of insulinoma refers to the concept of the "Whipple triad" - symptoms of hypoglycemia, confirmed low blood glucose concentrations, improvement in well-being when taking foods containing glucose. Clinical manifestations of insulinoma are presented in Fig. 1. The purpose of our study is to summarize and analyze current data on various approaches to the treatment of insulinoma. The review includes comprehensive information about currently available treatment methods (both surgical,

Materials and methods. Using the keywords "insulinoma", "treatment", "surgical treatment", "drug treatment", "target therapy" and their analogues in Russian, we selected and analyzed literature from such databases as: scientific electronic library elibrary.ru , Pubmed, Google Scholar, MedLine, Scopus and Web of Science. Articles were selected based on their significance for understanding the current state of the problem of treating insulinoma in comparison with the experience of past years, as well as prospects in the treatment of this type of NET. Abstracts and full-text versions of publications were studied. 60 articles were selected for analysis from 1973 to 2022, including 26 articles from the last five years (2017–2022).

Surgery. To treat insulinoma, surgical treatment is primarily used, after which in most cases there is recovery and no relapses. For benign insulinomas, surgical treatment is recommended, regardless of the location of the tumor. The choice of procedure (laparoscopic or open surgery) depends primarily on the size and location of the tumor. Laparoscopic resection can be performed for small insulinomas (up to 2 cm in size at the time of diagnosis); insulin located in the body or tail of the pancreas [9]; if the tumor is close to the pancreatic duct, the preferred tactic is open intervention [10].

Minimally invasive treatment methods. Alternative methods of treating insulinoma include alcohol ablation under endoscopic ultrasound control, radiofrequency ablation, and tumor embolization. Such treatments may be offered as an alternative to patients who refuse surgery, the elderly, patients in poor general condition, patients with a history of multiple abdominal surgeries, and those at increased risk of perioperative complications for other reasons. In 2006, the results of treatment using ethanol ablation were published [14]. The patient, 78 years old, was in serious condition, and therefore a decision was made to refuse surgical intervention. As an alternative, ethanol destruction was chosen - a total of 8 ml of 95% ethanol was injected into the tumor. The authors reported achieving durable clinical and biochemical remission and concluded that this method can be used in patients with contraindications to surgical treatment. Recent data reported that the clinical success rate for ethanol ablation of pancreatic NETs was 87.9% (95% CI: 66.2–96.4%), and postoperative complications occurred in 21.2% of subjects [15]. However, in

the presented study, the majority of pancreatic tumors were hormonally inactive. W. Paik et al. reviewed the effectiveness and safety of ethanol ablation of NETs. In this study, the proportion of patients with insulinoma was 3 out of 8 patients. Of the 8 patients, it was not possible to achieve remission in two patients - with a solid pseudopapillary tumor of the pancreas and with a functionally inactive NET, and the latter developed acute pancreatitis after ablation. Three patients with insulinoma achieved remission, one of them experienced abdominal pain after the intervention [16]. In 2018, S. Qin et al. proposed the use of lauromacragol ablation (the drug damages the endothelium, causing coagulative necrosis, which leads to vascular sclerosis) under ultrasound control as a method accompanied by a lower risk of side effects compared to surgery and ethanol ablation. Ultrasound-guided lauromacragol ablation was performed in 7 patients, and after the procedure, all of them showed improved health and biochemical remission, and there were no side effects [17]. Radiofrequency ablation (RFA) is another method that is used to treat pancreatic tumors, in particular neuroendocrine ones. According to a meta-analysis by S. Fegrachi et al., the effectiveness of RFA for locally advanced pancreatic cancer is comparable to the results of surgery followed by chemotherapy [18]. Treatment of insulinoma with RFA is accompanied by regression of clinical symptoms and tumor size [19, 20]. When performing RFA, side effects may also occur, for example, in the description of a clinical case by M. Kluz et al. A patient developed pancreatic necrosis during RFA of insulinoma, but the patient was subsequently successfully treated [20]. Another non-surgical alternative may be tumor embolization. In 2008 G. Rott et al. reported successful embolization of insulinoma in an 84-year-old patient. Embolization was performed with 2 ml of gelatin-bound trisacrylic particles with a diameter of 300-500 μm, diluted with 5 ml of contrast agent and 10 ml of saline. In the postoperative period, abdominal pain, pancreatitis and diabetes mellitus were noted, but all of them were transient and subsequently regressed. Clinical and biochemical remission without delayed complications was observed within a year [21]. Selective embolization can be used either alone or in combination with intra-arterial chemotherapy [10]. DRUG TREATMENT. One of the most important measures in the treatment of insulinoma is the recommendation for the patient to have frequent split meals in order to prevent attacks of hypoglycemia [22].

2. Complex therapy of malignants, including metastatically advanced insulin. For patients in whom the disease progresses despite taking somatostatin analogues and the tumor volume can be reduced by cytoreduction, treatment with molecular targeted drugs may be recommended: tyrosine kinase inhibitors (sunitinib, etc.) and mTOR inhibitors (everolimus, etc.) [1]. For patients with severe symptoms due to large tumor size or rapidly growing metastases, chemotherapy along with a somatostatin analogue is used as initial treatment. Depending on the degree of tumor differentiation, different treatment regimens are used [1].

Conclusion. The analysis of the literature demonstrated the variety of treatment methods for insulinoma available today. However, the most important of them remains surgical treatment. The choice of treatment tactics in the absence of the possibility of surgical intervention is often determined by the availability of this or that equipment in a particular medical organization. In drug treatment, the main role is given to somatostatin analogues and diazoxide. The study of new drugs remains an important task for scientists, among them the most promising are new generations of somatostatin analogues, targeted and chemotherapeutic drugs, especially for the treatment of malignant insulinoma. The rare incidence of this type of tumor makes it difficult to conduct randomized controlled trials and prospective studies. That is why practicing doctors and scientists need to maintain close contact and take into account the treatment experience of each patient, which will help in the future to develop effective treatment algorithms.

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