UDC 616.33/.34-006-008.8:577.175.7](048.8)
DOI http://doi.org/10.30978/GS-2024-3-63

ISSN 2786-5584 print
ISSN 2786-5592 online

Evolution of the doctrine of Zollinger–Ellison syndrome. Literature review

Y. A. Dibrova, M. S. Kryvopustov

Bogomolets National Medical University, Kyiv

✉ Mykola Kryvopustov: mykola.kryvopustov@gmail.com

Y. A. Dibrova, http://orcid.org/0000-0002-2833-1667
M. S. Kryvopustov, http://orcid.org/0000-0003-4978-4873

Zollinger–Ellison syndrome (ZES) is a rare pathology that does not have specific clinical manifestations and is not always diagnosed in time. This is attributed to doctors' insufficient awareness of this pathology and the limited availability of the necessary examination methods. Foreign literary sources on this problem are analysed. Historical data regarding the discovery of this pathology and the origin of the syndrome's name are provided. The epidemiology of the disease is highlighted. The most characteristic clinical manifestations and possible complications of ZES are described in detail. The characteristic changes in gastric acid production associated with this pathology and their diagnostic value (sensitivity and specificity) are presented. At the same time, indicators of both basal and maximal stimulated gastric acid production are significantly increased. The most important stage in the examination of patients with suspected ZES is the determination of blood gastrin levels. At the same time, it is shown that it is not always possible to make definitive judgements in support of ZES based on gastrin indicators. An absolute criterion in favor of ZES is fasting gastrin values of 1000 pg/ml or more. When gastrin levels are less than this indicator, tests using secretin or calcium gluconate have significant diagnostic value. In these circumstances, tests with secretin or calcium gluconate are mandatory. The information on the possible localization of gastrin, the incidence of malignant transformation, and the mechanism of metastasis is given. Methods of determining gastrin localization, sensitivity, and specificity are described in detail. Based on the findings, a differentiated treatment strategy for patients with ZES is provided. Indications and contraindications for surgical and medical treatment of patients with ZES are given. The prospects of a new treatment direction - the use of targeted radiotherapy - are shown. These patients require constant monitoring by a gastroenterologist and a surgeon and periodically undergo the necessary examinations.

Keywords
Zollinger–Ellison syndrome, treatment tactics, gastrin, examination algorithm.

ARTICLE • Received 2024-08-25 • Received in revised form 2024-09-23

Zollinger–Ellison syndrome (ZES) is a relatively rare and difficult-to-diagnose disease with no clear pathognomonic clinical manifestations.

In 1955, Robert M. Zollinger and Edwin Ellison (R. Zollinger and E. Ellison), American surgeons at Ohio State University Medical Centre, published a report on two patients who had recurrent multiple duodenal ulcers in the intestine that were resistant to antiulcer treatment and standard surgical interventions. Pronounced hypersecretion of hydrochloric acid and non-beta-cell pancreatic tumours were also reported. These authors were the first to associate gastric hypersecretion of hydrochloric acid and recurrent peptic ulcers with pancreatic islet non-beta-cell tumours [76]. Since then, this pathology has been referred to by the names of these scientists. ZES is characterised by the above-mentioned triad of symptoms.

Later, R. Gregory et al., 1960 [24] established a cause-and-effect relationship between the clinical manifestations of ZES and hyperproduction of gastrin, which is produced by a specific tumour — gastrinoma — and leads to pronounced hypersecretion of hydrochloric acid by the stomach. This publication marked the beginning of the investigation into this pathology. Many professionals, including geneticists and pathophysiologists, gastroenterologists, endocrinologists, surgeons, and oncologists, contributed their scientific and practical expertise

to this issue. The interest in ZES by specialists from various fields of medicine and biology indicates that this pathology is becoming more relevant in the global medical community. This, in turn, contributed to a more in-depth study of the pathology's etiology and pathogenetic mechanisms, as well as the development and implementation of new diagnostic methods and treatment technologies [24].

Gastrinoma is the second most common neuroendocrine tumour (NET) after insulinoma. In most cases, gastrinomas are sporadic (not familial, not hereditary). However, in approximately half of the cases, they are associated with the syndrome of multiple endocrine neoplasia type 1 (MEN 1). Various samples reveal that 20—61 % of patients with MEN 1 syndrome have gastrinoma with ZES, while 30—38 % of all gastrinoma patients have MEN 1 syndrome [6, 19].

Epidemiology. Gastrinoma is the second most common neuroendocrine neoplasia after insulinoma. In most cases, gastrinomas are sporadic (not familial, not hereditary). However, in approximately half of the cases, they are associated with the syndrome of multiple endocrine neoplasia type 1 (MEN 1). Thus, according to different samples, gastrinoma is found in 20—61 % of patients with MEN 1 syndrome, and conversely, MEN 1 syndrome is found in 30—38 % of all patients with gastrinomas [6, 19].

Gastrinoma is caused by genetic mutations that lead to the uncontrolled proliferation of hormonally active cells. At the same time, multipotent stem cells are the source of gastrin-producing NET development [11].

Among patients with idiopathic peptic ulcer disease of the stomach and duodenum, ZES, as the cause of ulcer formation (that is, this ulcer is essentially a symptomatic ulcer), is diagnosed in 0.1—1 %, and among patients with recurrent postoperative ulcers, in 2 % of cases [55].

The annual incidence of ZES is 0.3—4 cases per 1 million of the global population. According to the literature, sporadic gastrinomas (ZES) are usually detected at the age of 41 to 55 years. However, observations of these diseases are also described both in children aged 7 years and in elderly people aged 70—80 years [17].

Gastrinomas in MEN 1 (hereditary gastrinomas) usually occur in younger patients as multiple microgastrinomas with a predominant localization in the duodenum [15].

According to some authors, this pathology occurs more often in men than in women (ratio 3 : 2) [32].

However, there is another opinion according to which this pathology is diagnosed more often in women than in men [17].

According to other data, ZES is equally often diagnosed in both men and women [38].

Features of the clinical course. ZES lacks pathognomonic clinical manifestations that would allow for an unambiguous diagnosis of this pathology. However, the presence of some non-specific symptoms and clinical manifestations makes it possible to suspect ZES.

According to the literature, common nonspecific symptoms include abdominal pain (73—98 %), diarrhea (73—75 %), heartburn (44—56 %), and weight loss (7—53 %) [41]. Other symptoms are nausea, vomiting, and intestinal malabsorption [22].

In almost all cases, the initial clinical symptoms of ZES are mainly due to gastric hypersecretion of hydrochloric acid and hyperchlorhydria, leading to severe peptic ulceration and, in some cases, malabsorption and diarrhea [22].

What is more, with ZES, unlike ulcers caused by *Helicobacter pylori* or non-steroidal anti-inflammatory drugs, they often have atypical localization — the distal parts of the colon, the proximal part of the jejunum, the esophagus, as well as possible multiple ulcers of different localization, which are characterized by quite frequent complications — perforation, bleeding, penetration, stenosis [10].

Diarrhea is the second most common symptom of ZES after abdominal pain. In 3—10 % of cases, diarrhea can be the first and only manifestation of ZES. The development of chronic diarrhea in ZES is also based on hyperproduction of hydrochloric acid, which neutralizes pancreatic enzymes, accompanied by malabsorption [56].

Heartburn and episodes of vomiting with acidic stomach contents at the height of pain are also a characteristic clinical sign of ZES, which can lead to its reduction and some relief. In the future, this can also lead to the development of gastroesophageal reflux disease (GERD). According to the Los Angeles classification, the severity of GERD with ZES can vary from mild (A or B) grade to severe (C or D) grade, potentially leading to the development of complications such as esophageal stricture, Barrett's esophagus, esophageal-tracheal, or even esophageal-aortic fistula [43, 52].

Robinson A. M. et al. (2023) described two cases of esophageal perforation in patients with ZES, in which peptic stricture and esophageal ulcer developed as a result of gastroesophageal reflux. One of them developed an esophageal-aortic fistula, which led to a fatal outcome [52].

Despite the improvement of diagnostic techniques and increased awareness of doctors, it is not always possible to recognize ZES in time. It can take 4—8 years from the moment of the first symptoms to

the establishment of a diagnosis. At the same time, in connection with the widespread use of PPIs, the percentage of early diagnosis of ZES decreased by 62 % compared to the time when PPIs were prescribed much less often [36]. This is because PPIs mask the clinical picture of ZES, and these patients are often misdiagnosed as having irritable bowel syndrome or reflux disease [20].

A number of diagnostic techniques are used for timely recognition of this pathology. The study of gastric acid production indicators has enabled the establishment of specific parameters inherent in ZES, since almost all clinical manifestations of this pathology arise from the hypersecretion of hydrochloric acid due to constant stimulation by hypergastrinemia. Namely, the assessment of basal gastric acid output (BAO) and maximum stimulated gastric acid output (MAO) and their ratio was carried out according to the method developed by A. W. Kay [34].

In patients with ZES, the BAO level was increased by 4—6 times, and in some patients by more than 10 times compared to the norm. At the same time, an increased level of MAO was also observed [16].

Patients with sporadic ZES without previous acid-reducing surgical interventions (gastric resection, vagotomy) had a BAO level of ≥ 15 mEq/h. The sensitivity of this criterion is 90—98 % [39].

In patients after acid-reducing operations, the sensitivity for BAO ≥ 5 mEq/h was 81—100 %, for BAO ≥ 14.4 mEq/h — 73 %, and 37 % for BAO ≥ 19.2 mEq/h, respectively. At the same time, the specificity for the BAO criterion ≥ 5 mEq/h was 85 %, while for the other two aforementioned criteria, it was 100 % [54].

In practice, the BAO criterion of ≥ 15 mEq/h for patients without previous acid-reducing surgery, with a sensitivity of 91 %, and ≥ 5 mEq/h for patients with a history of such surgery, with a sensitivity of 100 %, is most often used to diagnose ZES [39].

The MAO criterion of ≥ 25 mEq/h in patients without acid-reducing surgery and ≥ 10 mEq/h after acid-reducing surgery had a sensitivity of 90 %. Moreover, such a criterion as the BAO/MAO ratio ≥ 0.6 had a sensitivity and specificity of over 80 % [41].

The following criteria were determined during the study of indicators of gastric acid production by the method of intragastric pH-metry. In patients with ZES after previous acid-reducing interventions on the stomach, the pH values ranged from 0.83 to 1.99 ($M = 1.14 \pm 0.04$), and in patients with an unoperated stomach, from 0.32 to 1.14 ($M = 1.05 \pm 0.06$). Moreover, the sensitivity of these indicators in both groups was 99 % [54].

The ratio of BAO/MAO indicators also has its own peculiarity in ZES. In particular, when the value of this ratio is ≥ 0.6, the sensitivity reaches 89 % with the same percentage of specificity [54].

The next criterion for assessing the secretory function of the stomach was the study of the volume of gastric output over a certain period of time. In patients with ZES, the volume of gastric acid production was 3—8 times greater than in patients with idiopathic duodenal ulcers or in the control group.

In particular, in patients with previous acid-reducing surgical interventions, the volume of gastric secretion was 247 ± 25 ml/h, and without gastric interventions, it was 314 ± 10 ml/h [8].

In patients with ZES, in the presence of diarrhea, peptic stricture of the esophagus, or cicatricial stenosis of the pyloric department, significantly higher rates of gastric acid production were observed compared to patients who did not have these symptoms. The presence or absence of abdominal pain, as well as symptoms such as heartburn, nausea, vomiting, weight loss, and bleeding, did not correlate with acid production [54].

Without a doubt, the main diagnostic criterion for the diagnosis of ZES is the determination of the level of gastrin in the blood serum. At the same time, it should be taken into account that the upper physiological level of fasting gastrin, according to various authors, can range from 100 pg/ml to 200 pg/ml. The content of gastrin from 300 pg/ml to 1000 pg/ml with the corresponding clinical picture is a reason to suspect ZES. And a level of more than 1000 pg/ml indicates the presence of a gastrinoma, provided that it is recorded in patients with peptic ulcer disease or hyperchlorhydria [2, 17].

Intermediate values of gastrin (200—1000 pg/ml) occur in 60 % of patients with ZES. At the same time, other potential causes of hypergastrinemia should be excluded. In particular, the secretion of gastrin in a normal physiological state is stimulated by distension of the antral part of the stomach, vagal stimulation, or hypercalcemia. However, it is inhibited by acidic gastric pH (negative feedback), secretin, somatostatin, vasointestinal polypeptide, glucagon, or calcitonin. Hypergastrinemia can also occur in other pathological conditions. Specifically, with hypochlorhydria or achlorhydria, chronic atrophic gastritis, pernicious anemia, or *Helicobacter pylori* infection [22].

Long-term use of proton pump inhibitors can also lead to hypergastrinemia. Therefore, before determining the level of gastrin, you should stop taking drugs in this group for at least 1 week, and H_2 histamine receptor antagonists — for 48 hours [54].

In 1972, J. I. Isenberg et al. established that in patients with ZES, there is a paradoxical increase in the level of gastrin in blood serum after intravenous injection of secretin [29].

Since then, this test has been widely implemented in practice and has acquired the status of a provocative secretin test. This test is indicated in controversial situations and for patients with suspected ZES when the fasting gastrin level does not exceed 1000 pg/ml [8].

Secretin is administered as a bolus intravenously (for 30 seconds) at a dose of 2 units/kg of body weight. Blood samples were tested for gastrin content fasting and 2.5, 5, 7.5, 10, 15, and 30 minutes after administration of secretin [22].

Different cut-off levels of gastrin increase have been proposed for evaluating the secretin test. In particular, the secretin test was considered positive with an absolute increase in gastrin concentration (by 110—200 pg/ml or more) or by 50 % of its fasting content. However, further studies revealed that an increase in serum gastrin of 120 pg/ml or more demonstrated high-test sensitivity (94 %) and 100 % specificity [22].

At the same time, false-negative results were observed in 6—20 % of patients, and false-positive results were observed in 15—39 % of cases. This could be due to the presence of pernicious anemia in patients or to their long-term use of proton pump inhibitors (PPIs). In 10 % of cases, the results of the secretin test in patients who have been taking proton pump inhibitors for a long time could be both false-positive and false-negative [57].

As an alternative to the secretin test, a test with intravenous infusion of calcium gluconate solution at a dose of 5 mg/kg/h over 3 hours was proposed. Blood samples for determination of gastrin concentration were examined before and after every 30-minute interval for 4 hours from the start of the infusion. The test results were considered positive when the gastrin level increased by 20 % or more compared to its fasting level [54].

The diagnostic value of indicators of general neuroendocrine markers (chromogranin-A, neuron-specific enolase, synaptophysin) is also limited by the fact that their specificity does not exceed 40—50 % [44].

However, the results of these techniques can be both false negative and false positive. Therefore, some difficulties in the evaluation of specific tumour markers in patients with gastrinoma require additional examination methods.

At the beginning of the study of ZES, it was considered that almost all sporadic gastrinomas are localized in the pancreas [28].

However, at the beginning of the 90s of the last century, systematic data on the localization of gastrin in the wall of the duodenum appeared. According to these sources, gastrinomas are three times more common in the pancreatic duct than in the pancreas [66, 76].

Characteristically, in 70—85 % of cases, duodenal gastrinomas are localized in the first and second portions of the duodenum. Duodenum gastrinomas are usually less than 1 cm in size, often multiple, and account for approximately 50—88 % of sporadic ZES-associated gastrinomas and 70—100 % of MEN 1 associated gastrinomas [49].

In 50 % of cases, gastrinoma is localized in the mucosa or submucosa of the duodenum [70].

Diametrical changes in the view of gastrin localization over the last few decades are certainly related to the improvement of instrumental diagnostic methods [31].

Given that gastrinomas of the duodenum were often small in size, mobilization of the duodenum, duodenotomy, and intraoperative transillumination of the duodenum are used for their careful search [18, 27, 64].

Characteristically, duodenal and pancreatic gastrinomas differ in their biological essence. In particular, pancreatic gastrinomas, unlike duodenal gastrinomas, have a much higher rate of liver metastases, which is one of the main factors in long-term survival, resulting in patients with pancreatic gastrinomas having a worse prognosis. Duodenal gastrinomas often metastasize to regional lymph nodes [13, 50, 67].

The results of further studies showed that about 80 % of gastrinomas are localized in an anatomical area called the gastrinoma triangle. Its vertices are the junction of the vesical and common bile ducts, the point of intersection of the middle and lower thirds of the duodenum, and the projection of the zone between the head and body of the pancreas [60].

Later, information appeared about the localization of gastrin in the lymph nodes of the abdominal cavity (primary lymphonodular gastrinoma). In particular, J. A. Norton et al. [49, 50] claimed that in 10—15 % of cases, primary gastrinomas are localized in peripancreatic and periduodenal lymph nodes. The possibility of primary localization of gastrin in lymph nodes is confirmed by the results of studies that report long-term (up to 20 years) recurrence-free survival after removal of only the lymph node in patients with sporadic ZES compared to patients after resection of primary duodenal or pancreatic gastrinoma [5, 12]. Primary sporadic gastrinomas can be localized not only in the pancreas, duodenum, and lymph nodes. In 5 % of cases, they were located in the ovaries, liver, biliary tract, stomach, kidneys, jejunum, and esophagus [13, 69].

According to the literature, primary localization of gastrin in the liver was observed only in 35 patients. Moreover, it is characteristic that in most of

the registered cases, there were single gastrinomas, and only 5 (14 %) had multiple tumours [25].

As a rule, gastrinoma metastasizes to the liver, regional lymph nodes, and bones. Metastases in the spleen, peritoneum, and mediastinum are less common. An important predictor of the presence of metastases in the liver is the localization of the tumour in the liver with a size of more than 3 cm [31].

Further diagnostic procedures are aimed at localization with gastrin. An important stage in the examination of a patient with ZES is the topical diagnosis of gastrinoma, which can be quite difficult.

Esophagogastroduodenoscopy (EGD) is used to visually assess the condition of the esophagus, stomach, and duodenum and to identify symptomatic ulcers of various locations and their possible complications. Duodenoscopy can also provide information about duodenal gastrinomas [17].

According to the literature, the sensitivity of transabdominal ultrasonography averaged 39 % (17—79 %) [9, 34].

Non-invasive imaging is primarily performed to assess the extent of the primary tumor or metastases. CT and MRI can detect tumors larger than 3 cm, but their results are questionable if the tumor is less than 3 cm [17]. According to D. V. Sahani [57] traditional imaging methods, which include computed tomography (CT) and magnetic resonance imaging (MRI), have low sensitivity that correlates with tumor size. Thus, the sensitivity does not exceed 20 % for gastrinomas less than 1 cm in size, 30—40 % for those between 1 and 3 cm, and exceeds 50 % for those more than 4 cm.

Computed tomography (CT) with contrast is informative in cases where the primary tumour is larger than 1 cm. When the tumour is located in the head of the pancreas and has metastases in the liver, the sensitivity is from 59 % to 78 %, and the specificity is from 95 % to 98 %, respectively. Conversely, the sensitivity decreases if the tumour is less than 1 cm, especially if it is located outside the pancreas [36].

MRI is considered one of the most sensitive imaging methods for liver and skeletal bone metastases in patients with NET and is recommended for monitoring the tumour's response to therapy. Contrast-enhanced MRI has shown a high specificity (namely, 100 %) in detecting small pancreatic gastrinomas and liver metastases, while its sensitivity varies from 25 % to 85 %. It should be noted that MRI showed a higher sensitivity for detecting liver metastases compared to CT [63].

Multidetector spiral computed tomography (MSCT) allows to detect a tumour in no more than 50 % of cases, and when the tumour size is less than 1 cm, the sensitivity decreases almost 2 times [34].

Endoscopic ultrasonography — endosonography (EUS), which allows detecting small tumours and determining their exact localization, has been widely used in the diagnosis of NET. The sensitivity of endoscopic ultrasonography in patients with NET pancreas is approximately 94 %, and in combination with computer tomography it reaches 100 % [9, 17].

Endoscopic ultrasound has become an important diagnostic test for the localization of gastrin, especially small (< 2 cm) pancreatic lesions. Its sensitivity and specificity are 75 %-100 % and 95 %, respectively, for pancreatic tumours. Unfortunately, its sensitivity sharply decreases in cases of duodenal localization, ranging from 38 % to 63 %. An additional advantage of this technique is the possibility of taking cytological/histological samples using a puncture/fine needle biopsy (FNA/B) to confirm the diagnosis of NET. False-negative results are possible mainly due to the low quality of the biopsy material. EUS-FNA/B is considered the primary technique for pancreatic tumour sampling, with a sensitivity of 80 % to 90 %, a specificity of 96 %, and a screening adequacy rate of 83—93 % [3, 73].

Endosonography is important in detecting multiple lesions of the pancreas in MEN 1 syndrome, as indicated by a number of authors, with a sensitivity of 55—88 %. However, despite the high efficiency of endoscopic ultrasonography (EUS), there are a number of limitations to its use. In particular, EUS has rather limited indications for tumor localization in the tail of the pancreas. This technique also has a low sensitivity for diagnosing duodenal gastrinoma. Tumour sizes less than 5 mm also significantly reduce the effectiveness of this method, especially in MEN 1 syndrome [62].

However, the results of using modern preoperative diagnostic methods to determine the prevalence of the tumour process make it possible to detect no more than 50 % of metastatic foci in the liver and less than 30 % of metastases up to 1.0 cm in size [14].

The informativeness of these diagnostic techniques in the recognition of extrahepatic metastases of NET (lymph nodes, peritoneum, bones, lungs) is even less [13].

Somatostatin receptor scintigraphy (SRS) is more sensitive than conventional imaging studies, including CT and MRI, and has a higher specificity for detecting extrahepatic gastrinoma. SRS involves the use of indium (In)-labeled octreotide, which has a strong affinity for somatostatin type 2 receptors found on gastrinoma cells and is called Octreoscan. This method showed quite good sensitivity (between 77 %-78 %) and good specificity (93 %-94 %) for detecting the primary tumour and

its metastases. However, sensitivity decreases for tumours smaller than 1 cm [61].

Visualization using PET-CT with 68 Ga-labelled somatostatin analogues has the highest sensitivity for the localization of P-NETs, as in general for other NETs, and also has a high specificity. In different studies of P-NETs, sensitivity ranged from 86 to 100 % (mean 93 %), and specificity ranged from 79 to 100 % (mean 96 %) for all P-NETs. This technique is particularly informative for localization of the primary tumour and determination of the stage of the disease, including metastases to other organs [40, 58, 68].

Non-invasive molecular imaging using positron emission tomography (PET) and somatostatin receptor (SSTR) indicators, combined with metabolic imaging using 2-[18F]Fluoro-2-deoxy-2-D-glucose (18 FDG), enables the evaluation of the tumour's structure and heterogeneity [58].

It is now well established that molecular PET/CT imaging using SSTR scanning in combination with FDG radioactive tracers plays a significant additional role in staging NET, changing its stage, and selecting patients for further treatment [45].

For localizing duodenal gastrinoma, the most informative method is transillumination [48].

Despite the availability of highly informative imaging methods, including radioisotope studies (scintigraphy with octreoscan, PET-CT with 68Ga), the localization of primary NET in 10—15 % of patients remains undetermined [71, 72].

Among the invasive examination methods aimed at establishing a diagnosis and determining the localization of the tumour, angiographic examination of the branches of the abdominal trunk and superior mesenteric artery, percutaneous transhepatic blood sampling with determination of the level of immunoreactive gastrin, as well as blood sampling from the hepatic veins after intra-arterial stimulation of various parts of the pancreas, are currently used. This is followed by the determination of the level of immunoreactive gastrin [7, 35].

However, even in patients with sporadic ZES and negative preoperative imaging studies, an experienced surgeon will detect gastrinoma in 98 % of patients, with 50 % achieving biological remission of the disease following surgery, which is comparable to the outcomes in patients with positive results [47].

Thus, in the vast majority of cases, modern methods of examination make it possible to diagnose ZES, determine the localization of gastrinoma, and develop a treatment strategy.

The main goals of drug therapy for ZES are to reduce the hypersecretion of hydrochloric acid as well as control the growth of the tumour and its metastases [4].

Currently, the «gold standard» of antisecretory therapy is the use of proton pump inhibitors (PPIs), the effectiveness of which has been proven in patients of this category [37, 39]. The main goal of using PPIs in patients with ZES is to achieve stable clinical and endoscopic remission. Various studies have shown that in patients with ZES, a reliable criterion demonstrating adequate control of the secretory function is BAO less than 10 mEq/h until the next dose of the drug [65].

In cases of ZES associated with MEN 1 syndrome, severe reflux esophagitis, or in patients after gastric surgery, the BAO levels should not exceed 5 mEq/h. To achieve the indicated goals of PPI therapy with an uncomplicated course of ZES, an initial dose equivalent to 60 mg/day of omeprazole is recommended. In other cases, the daily dose should be two times higher, divided into two doses (60 mg twice a day). If the level of BAO against the background of the indicated doses remains higher than 10 mEq/h, the PPI dose should be gradually increased and divided into 2 doses until the indicated goal is reached [4, 46].

Conservative treatment of PPIs with the correct dose selection ensures the absence of ulcer recurrence, which significantly affects the range of causes of mortality. Indeed, it contributed to a significant reduction in mortality from bleeding and perforations and an increase in the life expectancy of patients with ZES. In recent decades, the progression of the tumour process has caused more than half of the fatal consequences in patients with ZES [65].

The administration of synthetic analogues of somatostatin to patients with ZES not only suppresses the secretion of hydrochloric acid but also has an antitumour effect. The most common analogue of somatostatin on the market is octreotide. In addition, long-acting analogues of somatostatin (lanreotide, octreotide, somatulin, etc.) are now available. Their feasibility is determined by their comparable effectiveness at significantly lower cost. In a study involving 15 patients with ZES treated with somatostatin analogues, 53 % exhibited tumour advancement, 41 % experienced stabilisation, and just 6 % achieved tumour regression [59].

At one time, interferon-α (in a number of cases in combination with octreotide) was often used to stabilize the growth of pancreatic gastrin. According to the literature, interferon-α therapy led to the tumour's stabilization in 20—40 % of cases, and in 12 % of cases, its regression was observed [10].

The use of the technique of molecularly directed («targeted») therapy for the conservative treatment of NET has shown its effectiveness. In particular, this type of oncotherapy includes multitarget inhibitors of

receptors with tyrosine kinase activity (sunitinib) and mTOR inhibitors (everolimus, temsirolimus) [23].

The administration of sunitinib to 107 patients (66 with NET of the pancreas and 41 with carcinoid) resulted in tumour size reduction in 17 % of patients and stabilization in 68 %. In studies using mTOR inhibitors, the proportion of patients who responded to therapy was 7 % for temsirolimus and 15 % for everolimus [30].

Peptide-receptor radionuclide therapy (PRRT) is a promising direction in the treatment of NET. It is a highly targeted and effective form of radiopharmaceutical therapy (RFT) with minimal side effects for the treatment of NET with a large number of somatostatin receptors. In PRRT, the patient receives an intravenous injection of a drug such as octreotide (DOTATOC) and octreotate (DOTATATE) that is chemically bound to or radiolabelled with radioactive material, mainly lutetium-177. Somewhat less often, other radiopharmaceuticals, such as yttrium-90 or indium-111, are used. The radioactive drug binds octreotide to somatostatin receptors on tumour cells with subsequent irradiation and tumour regression [26].

Surgical treatment is indicated in patients with sporadic gastrinomas due to their high tendency to metastasize to the liver, lymph nodes, and distant organs. In cases where the process has progressed, preference should be given to nonsurgical treatment methods, including chemotherapy with everolimus, sunitinib, somatostatin analogues, interferon, chemoembolization, radioembolization, and radiofrequency ablation [51].

Currently, the primary treatment for sporadic gastrinoma, if technically feasible, involves either enucleation or local resection for damage to the pancreatic head or a distal pancreatectomy for distal pancreatic lesions. A Whipple resection is usually performed for large lesions of the pancreatic head or duodenum that cannot be adequately removed by enucleation [32, 37, 56].

Whipple's operation involves the removal of regional lymph nodes. This method allows for the detection of metastases in 30—70 % of patients when an isolated gastrinoma is located in the pancreatic head or in the case of duodenal gastrinomas. During the enucleation of gastrinomas, these metastases often remain unnoticed. Long-term results after Whipple's operation indicate an increase in the recurrence-free period with this surgical intervention [21].

However, after any type of surgical intervention, all patients with ZES should be monitored by a gastroenterologist to control the level of gastric acidity and blood gastrin, as well as, when necessary, adjust the PPI dose.

Thus, Zollinger-Ellison syndrome is a rare pathology that is quite difficult to diagnose. For a timely diagnosis, it is crucial to understand the characteristics of the clinical picture of this disease and have access to a comprehensive range of diagnostic methods that can identify effective therapeutic strategies. A multidisciplinary team must be involved in this process.

Declaration of interests

The authors declare no conflicts of interest.

Funding. The work is a fragment of the planned research work of the Department of General Surgery No.2 of Bogomolets National Medical University «Implementation of minimally invasive surgical techniques in the treatment of pathologies of the abdominal cavity, anterior abdominal wall and morbid obesity by fast-track technique» (State registration number 0118U000147).

Authors contributions

Y. A. Dibrova: writing the manuscript; M. S. Kryvopustov: work concept and design, critical review.

References

1. Alexander HR, Fraker DL, Norton JA, Bartlett DL, Tio L, Benjamin SB, Doppman JL, Goebel SU, Serrano J, Gibril F, Jensen RT. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. Ann Surg. 1998 Aug;228(2):228-38. doi: 10.1097/00000658-199808000-00013. PMID: 9712569; PMCID: PMC1191465.
2. Arnold R. Diagnosis and differential diagnosis of hypergastrinemia. Wien Klin Wochenschr. 2007;119(19-20):564-9. doi: 10.1007/s00508-007-0878-0.
3. Atiq M, Bhutani MS, Bektas M, Lee JE, Gong Y, Tamm EP, Shah CP, Ross WA, Yao J, Raju GS, Wang X, Lee JH. EUS-FNA for pancreatic neuroendocrine tumors: a tertiary cancer center experience. Dig Dis Sci. 2012 Mar;57(3):791-800. doi: 10.1007/s10620-011-1912-7. Epub 2011 Oct 1. PMID: 21964743.
4. Banasch M, Schmitz F. Diagnosis and treatment of gastrinoma in the era of proton pump inhibitors. Wien Klin Wochenschr 2007;119(19-20):573-8. doi: 10.1007/s00508-007-0884-2.
5. Bartsch DK, Waldmann J, Fendrich V, et al. Impact of lymphadenectomy on survival after surgery for sporadic gastrinoma. Br J Surg. 2012;99(9):1234-40. doi: 10.1002/bjs.8843.
6. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type I. Am J Med. 1994 Nov;97(5):436-44. doi: 10.1016/0002-9343(94)90323-9.
7. Berardi R, Torniai M, Savini A, Rinaldi S, Cascinu S. Gastro-entero-pancreatic neuroendocrine tumors: Is now time for a new approach? World J Clin Oncol. 2016 Apr 10;7(2):131-4. doi: 10.5306/wjco.v7.i2.131. PMID: 27081635; PMCID: PMC4826958.
8. Berna MJ, Hoffmann KM, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. Medicine (Baltimore) 2006;85(6):295-330. doi: 10.1097/01.md.0000236956.74128.76.
9. Birnbaum DJ, Gaujoux S, Cherif R, et al. Sporadic nonfunctioning pancreatic neuroendocrine tumors :prognostic significance of incidental diagnosis. Surgery. 2014;155(1):13-21. doi: 10.1016/j.surg.2013.08.007.
10. Campana D, Piscitelli L, Mazzotta E, Bonora M, Serra C, Salomone L, Corinaldesi R, Tomassetti P. Zollinger-Ellison syndrome. Diagnosis and therapy. Minerva Med. 2005 Jun;96(3):187-206. PMID: 16175161.
11. Capurso G, Festa S, Valente R, et al. Molecular pathology and genetics of pancreatic endocrine tumours. J Mol Endocrinol. 2012 Jun 26;49(1):37-50. doi: 10.1530/JME-12-0069.

12. Chen Y, Deshpande V, Ferrone C, et al. Primary lymph node gastrinoma: A single institution experience. Surgery. 2017 Nov;162(5):1088-94. doi: 10.1016/j.surg.2017.05.017. Epub 2017 Jul 10.
13. Daskalakis K, Alexandraki K, Kassi E, Tsoli M, Angelousi A, Ragkousi A, Kaltsas G. The risk of lymph node metastases and their impact on survival in patients with appendiceal neuroendocrine neoplasms: a systematic review and meta-analysis of adult and paediatric patients. Endocrine. 2020 Jan;67(1):20-34. doi: 10.1007/s12020-019-02072-y. Epub 2019 Sep 6. PMID: 31493274; PMCID: PMC6969007.
14. de Mestier L, Zappa M, Hentic O, Vilgrain V, Ruszniewski P. Liver transarterial embolizations in metastatic neuroendocrine tumors. Rev Endocr Metab Disord.2017 Dec;18(4):459-71. doi: 10.1007/s11154-017-9431-2.
15. Dralle H. Primäre Lymphknoten-gastrinome. Der Chirurg. 2019;90(Suppl 2):100. doi: 10.1007/s00104-019-0886-4.
16. Ellison EC, O'Dorisio TM, Woltering EA, et al. Suppression of gastrin and gastric acid secretion in the Zollinger-Ellison syndrome by long-acting somatostatin (SMS 201-995). Scand J Gastroenterol. 1986;21(Suppl 119):206-11. doi: 10.3109/00365528609087454.
17. Epelboym I, Mazeh H. Zollinger-Ellison syndrome:classical considerations and current controversies. Oncologist. 2014 Jan;19(1):44-50. doi: 10.1634/theoncologist.2013-0369.
18. Frucht H, Norton JA, London JF, et al. Detection of duodenal gastrinomas by operative endoscopic transillumination:a prospective study. Gastroenterology. 1990;99(6):1622-27. PubMed:2227278. doi: 10.1016/0016-5085(90)90466-e.
19. Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome:a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine (Baltimore). 2004 Jan;83(1):43-83. doi: 10.1097/01.md.0000112297.72510.32.
20. Gibril F, Jensen RT. Zollinger-Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion. Curr Gastroenterol Rep. 2004;6:454-63. doi: 10.1007/s11894-004-0067-5.
21. Giovinazzo F, Butturini G, Monsellato D, et al. Lymph nodes metastasis and recurrences justify an aggressive treatment of gastrinoma. Updates Surg. 2013;65:19-24. doi: 10.1007/s13304-013-0201-8.
22. Giusti F, Cioppi F, Fossi C, Marini F, Masi L, Tonelli F, Brandi ML. Secretin Stimulation Test and Early Diagnosis of Gastrinoma in MEN1 Syndrome: Survey on the MEN1 Florentine Database. J Clin Endocrinol Metab. 2022 Apr 19;107(5):e2110-e2123. doi: 10.1210/clinem/dgab903. PMID: 34922358.
23. Grande E, Rodriguez-Antona C, López C, Alonso-Gordoa T, Benavent M, Capdevila J, Teulé A, Custodio A, Sevilla I, Hernando J, Gajate P, Molina-Cerrillo J, Díez JJ, Santos M, Lanillos J, García-Carbonero R. Sunitinib and Evofosfamide (TH-302) in Systemic Treatment-Naïve Patients with Grade 1/2 Metastatic Pancreatic Neuroendocrine Tumors: The GETNE-1408 Trial. Oncologist. 2021 Nov;26(11):941-949. doi: 10.1002/onco.13885. Epub 2021 Jul 14. PMID: 34190375; PMCID: PMC8571752.
24. Gregory RA, Tracy HJ, French JM, Sircus W. Extraction of a gastrin-like substance from a pancreatic tumour in a case of Zollinger-Ellison syndrome. Lancet. 1960 May 14;1(7133):1045-8. doi: 10.1016/s0140-6736(60)90932-6.
25. Hanzawa S, Sadamori H, Kagoura M, Monden K, Hioki M, Hyodo T, Omonishi K, Takakura N. Primary hepatic gastrinoma being diagnosed preoperatively: a case report and literature review. Surg Case Rep. 2020 Nov 18;6(1):290. doi: 10.1186/s40792-020-01072-9. PMID: 33206240; PMCID: PMC7674545.
26. Harris E, Zhernosekov K. The evolution of PRRT for the treatment of neuroendocrine tumors; What comes next? Front Endocrinol (Lausanne). 2022 Oct 31:13:941832. doi: 10.3389/fendo.2022.941832.
27. Harper S, Carroll RW, Frilling A, Wickremesekera SK, Bann S. Primary lymph node gastrinoma: 2 cases and a review of the literature. J Gastrointest Surg. 2015;19(4):651-5. doi: 10.1007/s11605-014-2729-4. Epub 2015 Jan 27. PubMed:25623161.
28. Hofmann JW, Fox PS, Wilson SD. Duodenal wall tumors and the Zollinger-Ellison syndrome. Surgical management. Arch Surg. 1973 Aug;107(2):334-9. doi: 10.1001/archsurg.1973.01350200194040.
29. Isenberg JI, Walsh JH, Passaro E Jr, Moore EW, Grossman MI. Unusual effect of secretin on serum gastrin, serum calcium, and gastric acid secretion in a patient with suspected Zollinger-Ellison syndrome. Gastroenterology. 1972 Apr;62(4):626-31. PMID: 5020875.
30. Ito T, Igarashi H, Uehara H, Jensen RT. Pharmacotherapy of Zollinger-Ellison syndrome. Expert Opin Pharmacother. 2013 Feb;14(3):307-21. doi: 10.1517/14656566.2013.767332.
31. Ito T, Cadiot G, Jensen RT. Diagnosis of Zollinger-Ellison syndrome:increasingly difficult. World J Gastroenterol. 2012 Oct 21;18(39):5495-503. doi: 10.3748/wjg.v18.i39.5495.
32. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology. 2012;95(2):98-119. doi: 10.1159/000335591. Epub 2012 Feb 15. PMID: 22261919; PMCID: PMC3701449.
33. Jensen RT, Niederle B, Mitry E, et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology. 2006;84:17382. doi: 10.1159/000098009.
34. Kay AW. Effect of large doses of histamine on gastric secretion of HCI; an augmented histamine test. Br Med J. 1953 Jul 11;2(4827):7780. doi: 10.1136/bmj.2.4827.77. PMID: 13051582; PMCID: PMC2028464.
35. Koh YX, Chok AY, Zheng HL, Tan CS, Goh BK. A systematic review and metaanalysis of the clinicopathologic characteristics of cystic versus solid pancreatic neuroendocrine neoplasms. Surgery. 2014;156(01):8396. doi: 10.1016/j.surg.2014.03.026.
36. Kondo NI, Ikeda Y. Practical management and treatment of pancreatic neuroendocrine tumors. Gland Surg. 2014;3:27683. doi: 10.3978/j.issn.2227-684X.2013.12.05.
37. Krampitz GW, Norton JA. Current management of the Zollinger-Ellison syndrome. Adv Surg. 2013:47:5979. doi: 10.1016/j.yasu.2013.02.004.
38. Kunz PL, ReidyLagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, Jensen RT, Kim MK, Klimstra DS, Kulke MH, Liu EH, Metz DC, Phan AT, Sippel RS, Strosberg JR, Yao JC; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013 May;42(4):55777. doi: 10.1097/MPA.0b013e31828e34a4. PMID: 23591432; PMCID: PMC4304762.
39. Liebert H, Roth J. Contribution to the problem of the Zollinger-Ellison syndrome. Zentralbl Chir 1975;100(9):5604.
40. McGowan CC, Cover TL, Blaser MJ. Helicobacter pylori and gastric acid:biological and therapeutic implications. Gastroenterology. 1996 Mar;110(3):92638. doi: 10.1053/gast.1996.v110.pm8608904.
41. Mendelson AH, Donowitz M. Catching the Zebra: Clinical Pearls and Pitfalls for the Successful Diagnosis of Zollinger-Ellison Syndrome. Dig Dis Sci. 2017 Sep;62(9):2258-2265. doi: 10.1007/s10620-017-4695-7. Epub 2017 Aug 3. PMID: 28776139.
42. Metz DC, Cadiot G, Poitras P, Ito T, Jensen RT. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. Int J Endocr Oncol. 2017;4(4):167-185. doi: 10.2217/ije-2017-0018. Epub 2017 Oct 11. PMID: 29326808; PMCID: PMC5757869.
43. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors:pancreatic endocrine tumors. Gastroenterology. 2008;135:146992. doi: 10.1053/j.gastro.2008.05.047. PMID:18703061.
44. Miller LS, Vinayek R, Frucht H, Gardner JD, Jensen RT, Maton PN. Reflux esophagitis in patients with Zollinger-Ellison syndrome. Gastroenterology. 1990 Feb;98(2):341-6. doi: 10.1016/0016-5085(90)90823-j. PMID: 1967239.
45. Modlin M, Bodei L, Kidd M. Neuroendocrine tumor biomarkers: From monoanalytes to transcripts and algorithms. Best Pract Res Clin Endocrinol Metab. 2016 Jan;30(1):5977. doi: 10.1016/j.beem.2016.01.002.
46. Nagtegaal ID, Odze RD, Limstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020. Jan;76(2):1828. doi: 10.1111/his.13975.
47. Nieto JM, Pisegna JR. The role of proton pump inhibitors in the treatment of ZollingerEllison syndrome. Expert Opin Pharmacother. 2006 Feb;7(2):16975. doi: 10.1517/14656566.7.2.169.
48. Norton JA, Fraker DL, Alexander HR, et al. Value of surgery in patients with negative imaging and sporadic zollingerellison syndrome. Ann Surg. 2012;Sep;256(3):50917. doi: 10.1097/SLA.0b013e318265f08d.
49. Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, Jensen RT. Surgery increases survival in patients with gastrinoma. Ann Surg. 2006 Sep;244(3):410-9. doi: 10.1097/01.sla.0000234802.44320.a5. PMID: 16926567; PMCID: PMC1856542.

50. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases or survival in patients with ZollingerEllison syndrome? Ann Surg. 2004;May;239(5):61725; discussion 626. doi: 10.1097/01.sla.0000124290.05524.5e.
51. Norton JA, Alexander RH, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Possible primery lymph node gastrinoma: occurrence, natural history, and predictive factors. Ann. Surg. 2003 May;237(5):6507; discussion 6579. doi: 10.1097/01.SLA.0000064375.51939.48.
52. Phan J, Benhammou JN, Pisegna JR. Gastric Hypersecretory States: Investigation and Management. Curr Treat Options Gastroenterol. 2015 Dec;13(4):386-97. doi: 10.1007/s11938-015-0065-8. PMID: 26342486; PMCID: PMC4633316.
53. Poitras P, Gingras MH, Rehfeld JF. Secretin stimulation test for gastrin release in ZollingerEllison syndrome:to do or not to do? Pancreas. 2013;42:9034. PMID:23851427. doi: 10.1097/MPA.0b013e318298df75.
54. Robinson AM, McNeil MV, Stueck AE, Ermerak NO, Plourde M, French DG. Esophageal perforation in ZollingerEllison syndrome and the importance of assessing for aortogastric fistula: a report of two rare cases. AME Med J. 2023;8:39. doi: 10.21037/amj-23-48.
55. Roy PK, Venzon DJ, Feigenbaum KM, Koviack PD, Bashir S, Ojeaburu JV, Gibril F, Jensen RT. Gastric secretion in Zollinger-Ellison syndrome. Correlation with clinical expression, tumor extent and role in diagnosis--a prospective NIH study of 235 patients and a review of 984 cases in the literature. Medicine (Baltimore). 2001 May;80(3):189-222. doi: 10.1097/00005792-200105000-00005. PMID: 11388095.
56. Roy PK, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL, Gibril F, Jensen RT. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. Medicine (Baltimore). 2000 Nov;79(6):379-411. doi: 10.1097/00005792-200011000-00004. PMID: 11144036.
57. Sahani DV, Bonaffini PA, Castillo CFD, Blake MA. Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. Radiology. 2013 Jan;266(1):3861. doi: 10.1148/radiol.12112512.
58. Shah P, Singh MH, Yang YX, Metz DC. Hypochlorhydria and achlorhydria are associated with falsepositive secretin stimulation testing for ZollingerEllison syndrome. Pancreas. 2013 Aug;42(6):9326. doi: 10.1097/MPA.0b013e3182847b2e. PMID: 23851430; PMCID: PMC3712291.
59. Sharma P, Arora S, Mukherjee A, et al. Predictive value of 68GaDOTANOC PET/CT in patients with suspicion of neuroendocrine tumors:is its routine use justified? Clin Nucl Med. 2014;39:3743. PMID:24152621. doi: 10.1097/RLU.0000000000000257.
60. Shojamanesh H, Gibril F, Louie A, et al. Prospective study of the antitumor efficacy of longterm octreotide treatment in patients with progressive metastatic gastrinoma. Cancer. 2002 Jan 15;94(2):33143. doi: 10.1002/cncr.10195.
61. Stabile BE, Morrow DJ, Passaro JE. The gastrinoma triangle: operative implications. Am J Surg. 1984 Jan;147(1):2531. doi: 10.1016/0002-9610(84)90029-1. PMID: 6691547.
62. Stokkel MP, Rietbergen DD, Korse CM, Taal BG. Somatostatin receptor scintigraphy and chromogranin A assay in staging and followup of patients with welldifferentiated neuroendocrine tumors. Nucl Med Commun. 2011;32:7317. PMID:21633314. doi: 10.1097/MNM.0b013e328347a895.
63. Tamm E, Bhosale P, Lee JH, Rohren EM. State–of–the–art imaging of pancreatic neuroendocrine tumors. Surg Oncol Clin N Am. 2016;25(2):375400. doi: 10.1016/j.soc.2015.11.007.
64. Thoeni RF, MuellerLisse UG, Chan R, Do NK, Shyn PB. Detection of small, functional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. Radiology. 2000;214:48390. doi: 10.1148/radiology.214.2.r00fe32483.
65. Thom AK, Norton JA, Axiotis CA, Jensen RT. Location, incidence, and malignant potential of duodenal gastrinomas. Surgery. 1991 Dec;110(6):108691; discussion 10913. PMID: 1745977.
66. Tomassetti P, Campana D, Piscitelli L, et al. Treatment of ZollingerEllison syndrome. World J Gastroenterol. 2005 Sep 21;11(35):542332. doi: 10.3748/wjg.v11.i35.5423.
67. Thompson NW, Pasieka J, Fukuuchi A. Duodenal gastrinomas, duodenotomy, and duodenal exploration in the surgical management of ZollingerEllison syndrome. World J Surg. 1993 Jul-Aug;17(4):45562. doi: 10.1007/BF01655104.
68. Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, Gibril F, Metz DC, Fraker DL, Norton JA, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology. 1995 Jun;108(6):1637-49. doi: 10.1016/0016-5085(95)90124-8. PMID: 7768367.
69. Wong KK, Gandhi A, Viglianti BL, Fig LM, Rubello D, Gross MD. Endocrine radionuclide scintigraphy with fusion single photon emission computed tomography/computed tomography. World J Radiol. 2016 Jun 28;8(6):635-55. doi: 10.4329/wjr.v8.i6.635. PMID: 27358692; PMCID: PMC4919764.
70. Wu PC, Alexander HR, Bartlett DL, Doppman JL, Fraker DL, Norton JA, Gibril F, Fogt F, Jensen RT. A prospective analysis of the frequency, location, and curability of ectopic (nonpancreaticoduodenal, nonnodal) gastrinoma. Surgery. 1997 Dec;122(6):1176-82. doi: 10.1016/s0039-6060(97)90224-5. PMID: 9426435.
71. Yates CJ, Newey PJ, Thakker RV. Challenges and controversies in management of pancreatic neuroendocrine tumours in patients with MEN1. Lancet Diabetes Endocrinol. 2015 Nov;3(11):895-905. doi: 10.1016/S2213-8587(15)00043-1. Epub 2015 Jul 9. PMID: 26165399.
72. Zandee WT, Merola E, Poczkaj K, et al. Evaluation of multidisciplinary team decisions in neuroendocrine neoplasms: Impact of expert centres. Eur J Cancer Care. 2022;31(6):e13639. https://doi.org/10.1111/ecc.13639.
73. Zandee WT, de Herder WW. The evolution of neuroendocrine tumor treatment reflected by ENETS guidelines. Neuroendocrinology. 2018;106(4):35765. https://doi.org/10.1159/000486096.
74. Zilli A, Arcidiacono PG, Conte D, Massironi S. Clinical impact of endoscopic ultrasonography on the management of neuroendocrine tumors: lights and shadows. Dig Liver Dis. 2018;50:614. PMID:29102525. doi: 10.1016/j.dld.2017.10.007.
75. Zogakis ThG, Gibril F, Libutti SK, et al. Management and outcome of patients with sporadic gastrinoma arising in the duodenum. Ann Surg. 2003 Jul;238(1):428. doi: 10.1097/01.SLA.0000074963.87688.31.
76. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg. 1955 Oct;142(4):70923; discussion, 7248. PMID: 13259432; PMCID: PMC1465210.

Еволюція вчення про синдром Золлінгера — Еллісона. Огляд літератури

Ю. А. Діброва, М. С. Кривопустов

Національний медичний університет імені О. О. Богомольця, Київ

Сидром Золлінгера — Еллісона (СЗЕ) — рідкісна патологія, яка не має специфічних клінічних виявів та не завжди вчасно діагностується. Це зумовлено недостатньою обізнаністю лікарів щодо цієї патології та часто недоступністю необхідних методів обстеження. Проаналізовано зарубіжні літературні джерела з цієї проблеми. Наведено дані щодо відкриття цієї патології та походження назви синдрому. Висвітлено питання епідеміології захворювання. Детально описано найхарактерніші клінічні вияви та можливі ускладнення СЗЕ. Наведено зміни шлункової кислотопродукції, характерні для цієї патології, та їхнє діагностичне значення (чутливість і специфічність). При цьому значно підвищуються показники як базальної, так і максимальної стимульованої шлункової кислотопродукції. Найважливішим етапом обстеження пацієнтів із підозрою на СЗЕ є визначення рівня гастрину в крові, який значно підвищується за цієї патології. Однак за показником гастрину не завжди можна впевнено діагностувати СЗЕ. Абсолютним критерієм на користь СЗЕ є рівень гастрину натще ≥ 1000 пг/мл. Якщо цей показник < 1000 пг/мл, то значну діагностичну цінність мають тести із застосуванням секретину чи глюконату кальцію. Наведено дані про можливу локалізацію гастрином, частоту їх злоякісного переродження та шляхи метастазування. Детально описано методики визначення локалізації гастрином із зазначенням їхньої чутливості та специфічності. Висвітлено диференційовану тактику лікування хворих із СЗЕ на підставі результатів обстеження. Обґрунтовано необхідність постійного перебування цих пацієнтів під наглядом гастроентеролога та хірурга. Наведено диференційовану тактику лікування хворих із СЗЕ з урахуванням результатів обстеження, а також показання та протипоказання до хірургічного та медикаментозного лікування пацієнтів із СЗЕ. Висвітлено перспективи нового лікувального напрямку — застосування таргетної радіотерапії. Обґрунтовано необхідність для цих пацієнтів постійно перебувати під наглядом гастроентеролога та хірурга й періодично проходити необхідні обстеження.

Ключові слова: синдром Золлінгера — Еллісона, тактика лікування, гастрин, алгоритм обстеження.

FOR CITATION

Dibrova YA, Kryvopustov MS. Evolution of the doctrine of Zollinger-Ellison syndrome. Literature review. General Surgery (Ukraine). 2024;(3):63-72. http://doi.org/10.30978/GS-2024-3-63.