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Zollinger-Ellison Syndrome - review

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Abstract

Introduction and purpose

Zollinger-Ellison syndrome (ZES) is a constellation of symptoms that includes gastric ulcer, gastroesophageal reflux disease (GERD), and chronic diarrhea. They are caused by the presence of gastrinoma, which is a neuroendocrine tumor that secretes gastrin. Gastrinoma is

most often found in the duodenum and pancreas. ZES occurs sporadically in about 80% of cases, while in 20-25% it is a component of multiple endocrine neoplasms (MEN1). It is malignant in 60-90% of cases. The aim of the study is to present the typical clinical course of ZES, the diagnostic path and current therapeutic recommendations.
Description of the state of knowledge
ZES is present in about 0.1% -1% of patients with peptic ulcer disease. The direct cause of symptoms in patients with ZES is excessive gastric secretion stimulated by ectopic gastrin. Excess gastric acid damages the gastric mucosa and small intestine and disrupts the transport of fats, leading to the development of diarrhea. Other common symptoms include abdominal pain, nausea, or more rarely severe complications of GERD or peptic ulcer disease. Diagnostics include measurement of fasting serum gastrin, measurement of gastric pH, and assessment of basal gastric acid production.
Summary
In pharmacological treatment, proton pump inhibitors (PPIs) are the first-line drugs to control excessive gastric acid secretion in patients with ZES. Other therapeutic options include histamine receptor antagonists or somatostatin analogues. Surgical intervention remains the only possible causal treatment. In the case of sporadic ZES routine exploratory laparotomy with curative intent is recommended. In the group of patients with coexisting MEN-1 syndrome, surgical intervention is reserved for patients with tumors> 2 cm.

Key words: Zollinger-Ellison syndrome, gastrinoma, peptic ulcer disease, PPIs, gastrin

Introduction

Zollinger-Ellison syndrome (ZES) is a constellation of symptoms that includes gastric ulcer, gastroesophageal reflux disease (GERD) and chronic diarrhea.
They are caused by the presence of gastrinoma, which is a neuroendocrine tumor that secretes gastrin.

Gastrinoma is most often located in the duodenum, especially in its initial section and in the second place in the pancreas. It is rarely found elsewhere in the abdominal cavity, including the lymph nodes, stomach, mesentery, kidney capsule, spleen, net, ovary, and liver or bile

ducts. Less than 0.3% of primary tumors are found in extra-abdominal locations such as the heart and lungs. It is estimated that this tumor is malignant in 60-90% of cases.

ZES occurs sporadically in about 80% of patients, while in 20-25% it is a component of multiple endocrine neoplasms (MEN-1) - an autosomal dominant disorder characterized by neoplasms of several endocrine organs. Looking at the problem on the other hand, as many as 50% of people with MEN-1 are diagnosed with ZES at one of the stages of the disease. For the above reasons, MEN-1 syndrome should be included in the diagnostic path when diagnosing ZES [1,2].

Epidemiology

Due to the widespread use of proton pump inhibitors nowadays and masking the symptoms of reflux disease, it is difficult to accurately determine the incidence of ZES. It is estimated that ZES is present in about 0.1% -1% of patients with peptic ulcer disease, more often in women, without age predilection.
Gastrinoma is found in 0.1-3 people per million [1].

Pathophysiology

The direct cause of symptoms in patients with ZES is excessive gastric secretion stimulated by ectopic gastrin. Gastrin is a hormone produced by G cells in the pyloric part of the stomach and the initial part of the duodenum, which is responsible for stimulating the parietal cells to secrete hydrochloric acid.
According to a study by Robert T. Jensen and Tetsuhide Ito, fasting hyperergastrinemia results in up to 4- to 10-times increased basal gastric acid secretion (BAO).
The excess of gastrin also leads to a 4-6-times increase in the number of parietal and enterochromaffin-like cells. In some cases, the uncontrolled proliferation of enterochromaffin-like cells may lead to neoplastic transformation, starting with a simple hyperplasia, followed by linear, micronodular and adenomatous hyperplasia, eventually leading to dysplasia and the development of carcinoids.
The excess of gastric acid damages the gastric mucosa and the small intestine, which results in impaired transport of fats and inactivation of pancreatic lipase. These disorders result in the development of diarrhea, which affects up to 70% of patients suffering from ZES. Recent

studies show that in the course of ZES, bile acids can precipitate in the small intestine, which is manifested by fatty diarrhea [3].

Clinical picture

Symptoms in the course of ZES are initially non-specific and are sometimes underestimated. The most common complaint, reported by up to 70% of patients, is abdominal pain. Its causes are believed to be duodenal ulcer disease or, less frequently, gastroesophageal reflux disease.

More recent studies show a significant increase in the incidence of diarrhea among people with ZES, which affects more than 50% of patients, with 9-20% of patients being the dominant symptom. The diarrhea is low volume (<1 L/day) but high frequency. Sometimes it takes the form of mild fatty diarrhea. The presence of diarrhea is an important clinical indicator which, in combination with peptic ulcer disease, should suggest the diagnosis of ZES.

Problems related to GERD, such as heartburn, nausea, belching, are more and more often reported. Nausea and vomiting as well as weight loss are also more common symptoms. Weight loss may be caused by the negative effects of excess stomach acid on intestinal absorption and a reduction in appetite during the course of the disease. In advanced cases, neoplastic spreading also contributes to weight loss.

Currently, due to the widespread off-label use of PPIs, complications of advanced peptic ulcer disease rarely develop, such as peptic ulcer perforation, bleeding, and obstruction of the gastric outlet. Potential complications of GERD are also rarely encountered- esophageal stricture, bleeding, Barrett's esophagus or perforation of the esophagus with mediastinitis.

We cannot forget about the group of patients with ZES in the course of MEN-1 who develop additional abnormalities- hyperparathyroidism, pancreatic neuroendocrine neoplasms and pituitary adenomas. Appropriate selection of patients with MEN-1 is important because it affects all aspects of the disease, including the clinical picture, treatment approach, surgical intervention, prognosis, and the need for genetic counseling [3].

Diagnostics

It becomes more and more difficult to make a diagnosis of ZES, especially at an early stage, in times of widespread use of PPIs. PPIs can mask the characteristic symptoms of ZES as well as being the cause of the hypergastrinemia themselves.

The first test performed when ZES is suspected is the measurement of fasting serum gastrin. However, one should take into account the group of patients, which, incidentally, is much more common than ZES, with hypergastrinemia in the course of conditions such as chronic Helicobacter pylori infection, chronic atrophic gastritis, renal failure or the aforementioned use of PPIs. If the fasting gastrin level is normal, the test should be repeated. With a twice correct result, ZES can be ruled out with high probability (> 97%).

Hypergastrinemia can only be interpreted in conjunction with the measurement of gastric secretory capacity. It has been suggested that the way to identify the majority of patients with hypergastrinemia as potentially having ZES is to assess gastric pH, which in these patients was <2. To be reliable, this study requires the discontinuation of PPIs for a minimum of 7 days, which is potentially at risk of gastrointestinal complications [2].

The result of the gastrin level 10 times higher than the norm along with the decreased gastric pH allows for the diagnosis of ZES.
On the other hand, if the gastric pH is lowered, but the gastrin level is <10 times the norm, additional tests should be conducted, such as basal gastric acid production (BAO) or secretin text. For ZES, the BAO result> 15 mEq/h or the increase in serum gastrin >120 pg/ml after secretin administration is significant. For added reliability, PPI treatment should be discontinued during these studies as well [4].

Pharmacological treatment

Thanks to the discovery of histamine H2 receptor antagonists and PPIs, pharmacological control of gastric secretion is now possible in almost every patient, except in the rare case of patients who are unwilling or unable to take long-term medications. For this reason, total gastrectomy, formerly the only effective method in ZES, has now lost its importance.

H2 receptor antagonists, including cimetidine, ranitidine and famotidine, can be effectively used to control excessive gastric acid secretion in patients with ZES, however, they are often required at high doses and frequent dosing (every 4-6 hours). They maintained their effectiveness in the long-term evaluation, but required an average of at least one dose increase per year. According to comparative studies, described in the study of Tetsuhide Ito and others, famotidine has a 30% longer duration of action than cimetidine and ranitidine, which allows for less frequent dosing. Despite high doses, these drugs rarely cause side effects, except for the anti-androgenic effects of cimetidine, causing gynecomastia or impotence.

Currently, PPIs are the drugs of choice for the treatment of excessive acid secretion in patients with ZES. Due to their long duration of action, they can be dosed once a day in most patients.

All PPIs have been shown to be effective in the pharmacotherapy of ZES, including omeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole. The advantage of PPIs preparations is also the relative safety in long-term studies and the lack of the need to increase the dose. It is estimated that only 0.1% of patients had to discontinue PPI treatment due to any side effects. The effects of PPI-induced hypo- or achlorhydria appear to be a potential problem with long-term therapy. These include a decrease in the absorption of nutrients that require an acidic gastric environment- vitamin B12, iron, and calcium. Hypergastrinemia caused by PPIs can lead to the proliferation of enterochromaffin-like cells in the gastric mucosa, which has been associated with the development of gastric carcinoids in numerous animal models.There are reports that hypergastrinemia is also associated with an increased development of colon cancer, but there is no conclusive evidence for this yet.
It is currently recommended to start treatment with a dose corresponding to 60 mg/ day of ompreprazole and possibly reduce it over time under the control of disease symptoms, especially diarrhea and pain. Higher doses are required in patients with complicated disease [5].

Somatostatin analogues (SSAs), such as octreotide and lanreotide, effectively inhibit gastrin release and control excess gastric acid secretion. However, due to their parenteral form of administration, they are rarely used in the primary treatment of ZES. It is worth mentioning that there are reports of the anti-proliferative effect of SSAs due to the high expression of somatostatin receptors in gastrinomas. In a study described by Valentin Guarnott et al., There was a significant increase in progression-free survival in patients suffering from non-

functioning well-differentiated advanced neuroendocrine neoplasms. For this reason, the latest ENETS guidelines recommend the use of SSAs in patients who fail to undergo surgery to counteract tumor growth in advanced cases [6].

Surgical treatment

Surgical excision of gastrinoma is the only method of causal treatment of ZES, and removal of all lesions, both primary and metastatic, is still indicated in most cases. However, many aspects of the surgical procedure, such as the timing of the intervention, the extent of resection or the need for surgery in advanced disease, are controversial topics. The surgical approach also differs in sporadic Zollinger-Ellison syndrome and MEN-1 related ZES. More than half of gastrinomas are poorly differentiated and have a malignant potential, which significantly worsens the prognosis. For this reason, early surgical intervention and excision of primary lesions should be routinely performed to prevent tumor expansion [7].

ZES sporadic

In the case of sporadic ZES, in patients with a potentially resectable tumor, routine exploratory laparotomy with curative intent is recommended, unless surgery is contraindicated. According to a study by Qian-Qian Shao et al., the resection of an occasional gastrinoma resulted in a complete recovery in 50% -60% of patients, and the disease-free survival rate after 10 years was 35% -40%. Surgical resection in patients with ZES prevents the possibility of liver metastases and increases survival. If the location of the gastrinoma is not confirmed by preoperative tests, the decision to undergo surgery is controversial. This applies to approximately 30% of tumors in patients with sporadic ZES, including more than 60% of tumors $\leq$ 1 cm in size.

Sporadic gastrinomas located away from the pancreatic duct may be locally removed or enucleated. Wider resections are necessary for tumors less than 3 mm from the pancreatic duct. Due to the fact that the presence of possible liver metastases is an important prognostic indicator, intraoperative liver exploration is recommended. Lymphadenectomy should be performed routinely due to the frequency of nodal metastases [7].

ZES in the course of MEN-1

In the group of patients with coexisting MEN-1 syndrome, metastatic changes in the lymph nodes, multiple duodenal gastrinomas and other pancreatic neuroendocrine tumors are often found. For this reason, local resection or enucleation rarely leads to long-term healing. The current recommendations of many societies, including ENET, NANETs and Endocrine, recommend conservative treatment of small neuroendocrine tumors (<1.5–2 cm) in patients with ZES in the course of MEN-1 and their close monitoring. Surgical intervention is reserved for patients with tumors >2 cm.

Surgical alternatives in advanced patients include excision of gastrinoma of the head of the pancreas, limited surgical resection of the tumor with excision of the duodenal lesions, and distal pancreatectomy. However, this approach is associated with a risk of relapse and a low cure rate. Intraoperative monitoring of gastrin levels may be helpful in determining the extent of resection.

Patients with advanced, unresectable metastatic disease are eligible for non-surgical therapeutic procedures such as tyrosine kinase inhibitors, peptide radioreceptor therapy using somatostatin analogues, chemotherapy or embolization of liver lesions [8].

Summary

All PPIs have been shown to be effective in the pharmacotherapy of ZES, including omeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole, and are the first-line treatment. The advantage of PPI preparations is their relative safety in long-term studies and the lack of the need to increase the dose.
H2 receptor antagonists, including cimetidine, ranitidine and famotidine, can also be used effectively to control excessive gastric acid secretion in patients with ZES, however frequent dosing (every 4-6 hours) at high doses is necessary.
Somatostatin analogues (SSA), such as octreotide or lanreotide, due to the parenteral form of administration, are rarely used in the basic therapy of ZES, but due to their antiproliferative effect, they have been used in the treatment of patients who are not eligible for surgery in order to counteract tumor growth in advanced patients cases.

Surgical intervention remains the only possible causal treatment. In the case of sporadic ZES, in patients with a potentially resectable tumor, routine exploratory laparotomy with curative intent is recommended, unless surgery is contraindicated. In the group of patients with coexisting MEN-1 syndrome, surgical intervention is reserved for patients with tumors> 2 cm.

Contribution of authors:

J. Metelski- study concept and design; critical revision of the manuscript for important intellectual content; study supervision;

A.Metelska- acquisition of data; analysis and interpretation of data; technical support;

D.Sereda- acquisition of data; analysis and interpretation of data; technical support;

H.Nieścior- acquisition of data; analysis and interpretation of data; technical support

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