Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 8 (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Zollinger-Ellison Syndrome: An Overview

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Cite this paper as: Tolstykh Anton Alekseevich, Kazaryan Artem Sosovich, Isaeva Gunel Mardankyzy, Pershina Anna Alekseevna, Ilyasov TukhtasinAnvarzhonovich, Popova Olesya Dmitrievna, Kudryashova Ekaterina Nikolaevna, Kostina Marina Alekseevna, (2025) Zollinger-Ellison Syndrome: An Overview. *Journal of Neonatal Surgery*, 14 (8), 164-176.

ABSTRACT

Zollinger-Ellison syndrome is characterized by severe manifestations, including abdominal pain associated with duodenal peptic ulcer disease, gastroesophageal reflux disease, diarrhea, and weight loss. The underlying cause of the disease is a gastrin-producing tumor, which increases gastric acid secretion. The use of proton pump inhibitors may alleviate symptoms but complicate the accurate diagnosis of the condition. As a result, the average diagnostic delay for Zollinger-Ellison syndrome is several years. By the time the correct diagnosis is established, many patients have advanced gastrinoma with metastases to the liver and lymph nodes. Treatment at this stage is challenging and involves various surgical and therapeutic approaches. The aim of this study is to review current methods for diagnosing and treating patients with Zollinger-Ellison syndrome.

Methods: A search of publications in the databases PubMed, CYBERLININKA, and Google Scholar was conducted.

Results: Advancements in surgical and conservative treatment strategies, as well as the introduction of new techniques such as vascular embolization, radiopharmaceutical therapy, and chemotherapy, have improved cure rates, increased overall survival, and prolonged recurrence-free survival in patients with Zollinger-Ellison syndrome.

Conclusions: 1) Since Zollinger-Ellison syndrome is based on gastrin hypersecretion by a tumor, essential diagnostic steps should include serum gastrin measurement, gastric juice pH analysis, and tumor localization.

2) Studies on the immunohistological characteristics of gastrinomas have led to the development of diagnostic and therapeutic methods based on somatostatin analogs.

3) Surgical treatment of sporadic gastrinomas in Zollinger-Ellison syndrome has a high success rate. However, in advanced cases with metastases, surgical intervention is supplemented by vascular embolization, chemotherapy, and radiopharmaceutical therapy.

1. INTRODUCTION

Zollinger-Ellison syndrome (ZES) was first described in 1955 when two surgeons, R.M. Zollinger and E.H. Ellison, reported two cases involving non-beta-cell adenomas of the pancreas. These adenomas were identified during an autopsy (case 1) and a total gastrectomy (case 2) in the absence of clinical or laboratory symptoms. These pancreatic islet cell adenomas were associated with "almost incredible" levels of 12-hour nocturnal gastric secretion, despite complete vagotomy and radical gastric resection. In their publication, the authors hypothesized the potential role of a pancreatic tumor in the etiology of peptic ulcer disease and the marked increase in gastric acid secretion (1). This gradually led to the recognition of the link between Zollinger-Ellison syndrome (ZES) and gastrinoma.

Zollinger-Ellison syndrome (ZES) is caused by a neuroendocrine tumor, gastrinoma, which leads to severe, treatment-resistant peptic ulcer disease and other significant manifestations. Active investigation of ZES began in the 1970s, facilitated by advancements in physiology and the development of instrumental diagnostic techniques, which provided a clearer understanding of the disease's nature. Despite numerous breakthroughs, the diagnosis of ZES paradoxically became more challenging due to the advent and widespread use of antisecretory therapy, particularly proton pump inhibitors. Additionally, the prevalence of *Helicobacter pylori* infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have increased the frequency of conditions complicating the differential diagnosis of ZES. The reduced diagnostic efficiency and significant delays in establishing a definitive diagnosis—sometimes spanning several years—often result in the detection of gastrinomas at the metastatic stage (2).

Since the clinical elucidation of the etiology and pathogenesis of ZES, strategies for diagnosing and treating the disease have undergone significant changes. These developments are attributable not only to the aforementioned therapies but also to the advancement of novel laboratory diagnostics, instrumental imaging methods, surgical techniques, and accumulated clinical experience.

The aim of this study is to review current methods for diagnosing and treating patients with Zollinger-Ellison syndrome.

2. MATERIALS AND METHODS

To achieve the study objectives, a literature search was conducted using the PubMed, CYBERLENINKA, and Google Scholar databases. The search covered publications from the past 15 years. Articles were selected for review if they were open access and relevant to the topic. The selection process involved several stages: analysis of titles, analysis of abstracts, and analysis of full-text articles. At each stage, low-informative, irrelevant, duplicate, and commercial publications were excluded. The final reference list comprised 52 articles, of which 4 were in Russian and 48 in English.

3. RESULTS AND DISCUSSION

Zollinger-Ellison Syndrome: Definition and Epidemiology

Zollinger-Ellison syndrome (ZES) is a condition characterized by a group of symptoms, including severe peptic ulcer disease, gastroesophageal reflux disease (GERD), and chronic diarrhea, caused by a gastrin-secreting tumor (gastrinoma) located in the duodenum or pancreas (the "gastrinoma triangle"). This tumor leads to hyperstimulation of the acid-secreting cells in the stomach. A gastrinoma is a functional neuroendocrine tumor that secretes gastrin, thereby stimulating gastric acid production. Gastrinomas occur in the duodenum three times more frequently than in the pancreas. ZES is identified in approximately 0.1–1% of patients with peptic ulcer disease. Around 75% of gastrinomas are sporadic, while 25% of cases are associated with multiple endocrine neoplasia type 1 (MEN1).

Other neuroendocrine tumors can also produce gastrin, but not in sufficient quantities to cause the symptoms characteristic of ZES. Gastrinomas that produce the clinical presentation of ZES occur in approximately 80% of cases. Among patients with MEN1, gastrinomas with ZES are observed in 50% of cases. Therefore, individuals with MEN1 should undergo evaluation for gastrinoma (3, 4). MEN1 has an incidence of 1–2 cases per 100,000 people annually, with ZES associated with MEN1 accounting for 0.5–1 case per 100,000 people. MEN1 is caused by a mutation in the menin gene, which primarily affects the parathyroid gland (nearly 100% of cases) and is associated with neuroendocrine tumors of the pancreas (80% of cases), gastroduodenal tumors, pituitary adenomas, lipomas, and subepithelial or submucosal tumors (5). In MEN1, due to parathyroid gland involvement, ZES may arise as a result of hypercalcemia.

On average, eight years elapse between the onset of symptoms and the diagnosis of ZES. This delay is largely attributed to the prolonged use of proton pump inhibitors (PPIs). Before the widespread adoption of PPIs in clinical practice, referrals for ZES-specific diagnostic evaluations in the U.S. and Italy were 62% higher (3).

In sporadic ZES, gastrinomas occur in the duodenum in 60–80% of patients. In patients with ZES/MEN1, gastrinomas also predominantly arise in the duodenum (90–100%) and much less frequently (0–15%) in the pancreas. In sporadic ZES, gastrinomas may occasionally develop in the liver (<1%) and the hepatobiliary system. Gastrinomas in these locations and in the duodenum may be small (<0.5 cm) and multiple, making the use of sensitive imaging modalities, particularly during the preoperative period, essential (6).

Clinical Presentation

While the terms "gastrinoma" and "Zollinger-Ellison Syndrome (ZES)" are often used interchangeably, historically, ZES has been associated with the clinical manifestations of a neuroendocrine tumor secreting gastrin. However, certain gastrinomas do not produce sufficient quantities of biologically active gastrin, which results in the absence of symptoms typically associated with ZES. The primary pathological effects in ZES are caused by excessive gastric acid production, with basal acid output increased by 6–8 times (and sometimes over 10 times) and peak acid output elevated due to gastrinoma-induced stimulation of parietal cells, enterochromaffin-like cells, and other mucosal cells of the stomach lining (7).

The clinical presentation of ZES is driven by the effects of excessive acid secretion and manifests as abdominal pain due to peptic ulcer disease (73–98%), heartburn (44–56%), diarrhea (65–75%), weight loss (7–53%), and complications such as bleeding, strictures, perforation, or penetration (7, 8). The frequency of complications has decreased with modern treatments and does not exceed 30% (9). In 3–10% of patients, diarrhea may be the sole symptom of ZES (8). Disease onset can present as abdominal pain syndrome in the absence of *Helicobacter pylori* infection (as determined by urease testing and monoclonal antigen detection) and nonsteroidal anti-inflammatory drug (NSAID) use (as reported in patient history). Episodes of vomiting acidic gastric contents may also occur. Given these manifestations, conservative treatment focuses on controlling gastric acid hypersecretion.

In 49–61% of patients, signs of gastroesophageal reflux disease (GERD) are present at the time of ZES diagnosis. Reflux esophagitis may vary in severity, with complications including esophageal strictures and Barrett's esophagus. In 18–29% of ZES patients, no ulcers are detected at diagnosis, which may be attributed to periods of remission and the use of proton pump inhibitors (PPIs) (9, 10).

Diagnostics

The diagnosis of Zollinger-Ellison Syndrome (ZES) presents significant challenges due to its substantial overlap with multiple endocrine neoplasia type 1 (MEN1) and the ability of numerous other pathological conditions to mimic ZES, exhibiting similar symptoms.

Modern biochemical diagnostics of ZES involve the following steps:

1. Serum Gastrin Levels (Fasting Serum Gastrin, FSG):

In cases of suspected ZES, the first step is to determine fasting serum gastrin (FSG) levels. In the absence of antisecretory therapy, the sensitivity of this method reaches 98–100%. If FSG is not elevated, the test is repeated. If it remains within normal limits upon repeat testing, ZES can be excluded with 97% certainty. An elevated FSG necessitates proceeding to the next diagnostic stages.

2. Gastric Secretory Capacity (pH Measurement):

Gastric pH is assessed to confirm the presence of inappropriate hypergastrinemia. Antisecretory therapy (proton pump inhibitors, PPIs) should be discontinued at least seven days prior to testing. It is advisable to monitor the patient during this period, as increased gastric acidity poses risks.

3. FSG > 10x Normal Levels and Low pH:

If FSG is elevated more than tenfold (>1000 pg/mL, with normal levels <100 pg/mL) and gastric pH is ≤2, ZES is confirmed (excluding retained gastric antrum syndrome based on patient history).

4. FSG < 10x Normal Levels and Low pH:

If FSG is elevated but less than tenfold (>100 pg/mL, with normal levels <100 pg/mL) and gastric pH is ≤2, further tests, such as the secretin stimulation test or basal acid output, are recommended. In some clinics, advanced imaging methods like 68Ga-DOTATATE PET/CT (positron emission tomography/computed tomography) are used as alternative diagnostic approaches.

5. Secretin Stimulation Test:

This test, conducted while the patient is on PPIs, demonstrates an increase in serum gastrin >120 pg/mL and has a sensitivity of 94% and specificity of 100% for ZES. Basal acid output >15 mEq/h (in patients without prior gastric surgery) or >5 mEq/h (in patients after acid-reducing gastric surgery), combined with changes in FSG and pH described in Step 4, confirm the diagnosis of ZES (11).

Since hypergastrinemia can occur in conditions other than ZES, accurate differential diagnosis is crucial (Table 1).

Table 1: Causes of Hypergastrinemia (11)

Gastrin/pH	Causes
I. Physiological Hypergastrinemia with Achlorhydria/Hypochlorhydria	1. Chronic atrophic gastritis/pernicious anemia (common) 2. Treatment with potent acid-suppressing agents (especially proton pump inhibitors, PPIs) (common) 3. Chronic kidney failure (rare) 4. Pangastritis, H. pylori infection (common) 5. Previous gastric acid-reducing surgery/vagotomy (rare)
II. Inappropriate Hypergastrinemia with Hyperchlorhydria	1. H. pylori infection, predominantly in the antral region (common) 2. Gastric outlet obstruction 3. Hyperfunction/hyperplasia of antral G-cells (rare) 4. Chronic kidney failure (rare) 5. Short bowel syndrome (rare) 6. Gastric stasis syndrome (rare) 7. Juvenile gastric polyposis (rare) 8. Zollinger-Ellison syndrome (rare)
III. Analytical Error	

In the vast majority of cases, when the search algorithm is correctly performed, it is possible to adequately reject all incorrect diagnoses.

Secretin Provocation Test

The secretin stimulation test allows for the differentiation of Zollinger-Ellison syndrome (ZES) from other hypergastrinemic conditions. The principle of the method is based on the stimulation of gastrinoma cells by secretin, which leads to an increase in gastrin secretion while inhibiting normal G-cells. Rapid intravenous administration of 4 µg/kg secretin over 1 minute is followed by the assessment of gastrin levels at specific intervals after the infusion (12). In a clinical study, the secretin stimulation test revealed hypergastrinemia in 27.8% of patients with multiple gastroenteropancreatic neuroendocrine tumors. The test allows for the identification of positively stimulated hypergastrinemia in 75.0% of patients with normal fasting serum gastrin levels [13]. No significant impact of proton pump inhibitors (PPIs) on the test's sensitivity, specificity, or positive predictive value was observed [14].

Chromogranin A (CgA)

CgA is involved in various pathological conditions and diseases, both benign and malignant. It is associated with oncological diseases of the breast, intestines, ovaries, pancreas, prostate, hepatocellular carcinoma, as well as neuroendocrine tumors. CgA levels may increase in kidney diseases, use of proton pump inhibitors (PPIs) (due to elevated gastrin levels against the backdrop of hypochlorhydria), and in atrophic gastritis. The overall sensitivity of CgA in diagnosing neuroendocrine tumors is 60-80% and depends on the primary tumor localization, differentiation grade, and disease status [15]. An elevated serum level of chromogranin A is indicative of gastrinoma (16). Additionally, chromogranin A can be detected in tumor biopsy specimens through immunostaining (17, 18).

In some cases, the diagnosis of Zollinger-Ellison syndrome (ZES) is incorrectly made in patients with cholecystokinin-producing tumors (CCKoma), in whom the disease manifests as severe diarrhea, weight loss, recurrent duodenal ulcers, persistent gallbladder spasms, and gallstones. The diagnosis is complicated by the high homology between cholecystokinin and gastrin (cross-reactivity). In suspected CCKoma, three tests are recommended: for sulfated CCK peptides, non-sulfated CCK peptides, and gastrin (19).

In their publication, R.E. Rossi et al. proposed a detailed algorithm for the differential diagnosis of ZES (Fig. 1).

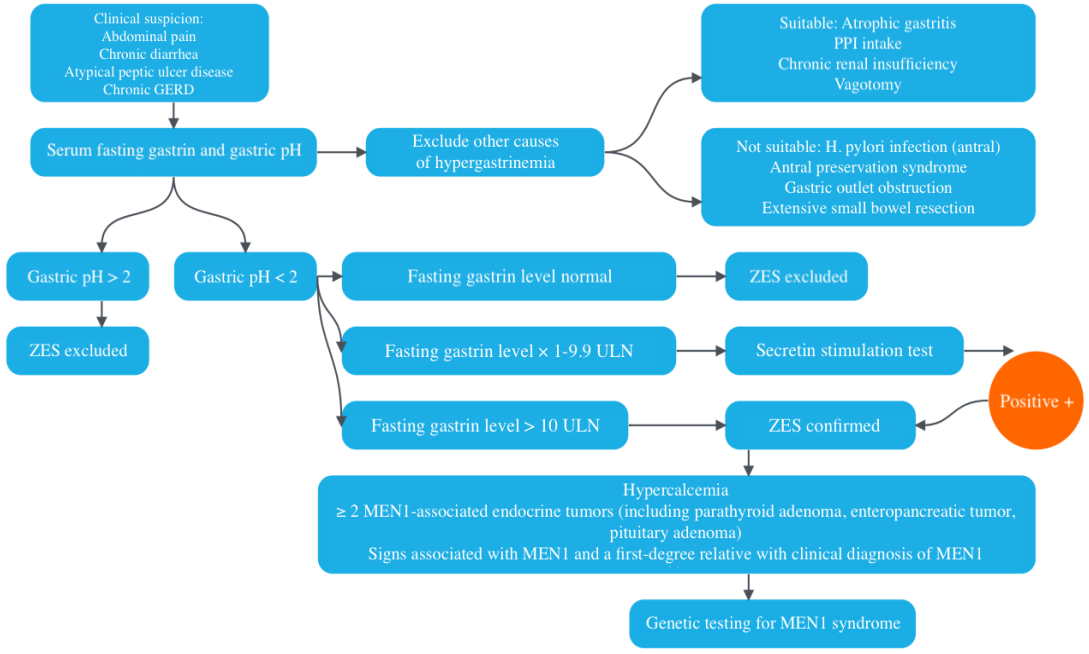

Figure 1: Diagnostic algorithm for suspected ZES (ULN – Upper Limit of Normal) (8)

The diagnosis of the tumor itself involves instrumental methods such as ultrasound of the abdomen (sensitivity % for the tumor and % for metastases): 6-70% and 14-76%; CT (33-100% and 35-100%); MRI (21-100% and 67-100%); selective abdominal angiography (sensitivity 35-100%); somatostatin receptor scintigraphy (58-77% and 88-100%); endoscopic ultrasound (sensitivity 40-100%); intraoperative ultrasound (sensitivity 80-100%) (9).

Endoscopy

In endoscopic examinations of patients with ZES, erosions and ulcers are found, often multiple ulcers in unusual locations, such as beyond the first or second part of the duodenum. Enlarged gastric folds are visualized in more than 90% of ZES patients (8).

Computerized Tomography (CT)

When ZES is suspected, diagnostic efforts focus on locating the tumor and its metastases. Contrast-enhanced CT is useful in detecting primary tumors larger than 1 cm, pancreatic head tumors, and liver metastases with a sensitivity of 59-78% and specificity of 95-98%. For tumors smaller than 1 cm in diameter and extrapancreatic locations, CT effectiveness decreases (8). Multislice CT allows for the detection of gastrinomas in the abdominal cavity, which may be adjacent to the duodenum. The size of primary duodenal tumors ranges from 0.2 cm to 2 cm in diameter, while extrapancreatic gastrinomas are larger (more than 2 cm) and typically located close to the duodenum [20]. Gastrinomas are occasionally found in the thoracic cavity (21). CT and MRI methods help visualize perigastriac lymphadenopathy and liver metastases in advanced cases (22).

MRI with contrast enhancement

Magnetic resonance imaging (MRI), alongside CT and other instrumental methods, is used when ZES is suspected (23). In some cases, when the gastrinoma is located atypically, MRI may be more effective than CT and endoscopic ultrasound (EUS) (24). MRI is considered one of the most sensitive methods for visualizing liver and bone metastases in patients with neuroendocrine tumors (25). MRI with contrast enhancement shows high specificity (100%) in detecting small pancreatic tumors and liver metastases, while its sensitivity is lower than optimal (25-85%). However, MRI sensitivity is higher than CT for liver metastases (8).

Scintigraphy

Somatostatin receptor scintigraphy using 111-indium-labeled octreotide is effective for assessing the size of gastrinomas and metastases. The recently introduced PET/CT imaging method using somatostatin radiopharmaceuticals labeled with 68Gallium (68Ga) (^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE) has shown high diagnostic effectiveness (26). Somatostatin receptor scintigraphy enables detection of the primary localization of gastrinomas in 58-77% of cases, and the presence of metastases in more than 88% of cases [27].

Single Photon Emission Computed Tomography (SPECT)

Single photon emission computed tomography (SPECT), along with somatostatin receptor scintigraphy (using 111-indium-pentetreotide), demonstrates the highest sensitivity in determining the location of tumors and searching for metastases (27).

Endoscopic Ultrasound (EUS)

Preoperative localization of neuroendocrine tumors of the pancreas is not achieved in approximately half of the patients. Endoscopic ultrasound (EUS) shows high sensitivity in detecting such tumors. In the study by M.A. Anderson et al., out of 54 cases with surgical confirmation of pancreatic tumors in 50 patients (93%), EUS correctly localized the tumor. The tumors identified included 29 insulinomas, 18 gastrinomas, as well as one glucagonoma, one carcinoid tumor, and one somatostatinoma. The most common location for the tumors was the head of the pancreas (46 patients) (28). Endoscopic ultrasound demonstrated 83% sensitivity for pancreatic gastrinomas; however, sensitivity was significantly lower for gastrinomas localized in the duodenum (12).

Esophageal pH Monitoring

Given the presence of GERD, patients with ZES may require esophageal pH monitoring, which detects episodes of acid reflux (a drop in pH below 4), a large number of such episodes, and prolonged periods of decreased pH both with and without proton pump inhibitors (PPIs) (29). This pattern may indicate abnormally excessive gastric acid production, prompting further diagnostic investigation.

Treatment

Zollinger-Ellison syndrome (ZES) increases mortality and significantly reduces the quality of life of patients. The complexities of treating ZES require close collaboration among the multidisciplinary team to plan and implement the most effective treatment strategies.

There are two main directions in the treatment of ZES:

1) Elimination/neutralization of excessive gastric acid secretion.

2) Removal of the tumor tissue (60-90% of gastrinomas are malignant).

Although surgical treatment has the potential to address both of these issues, in real clinical practice, less than 50% of patients with ZES are surgically cured (7).

Before the advent of effective modern medications, complications associated with acid hypersecretion were the primary cause of death in patients with ZES. Most often, fatal outcomes were associated with bleeding, penetration, perforation, fistula formation, and other issues. These occurred in the absence of adequate control of acid secretion. Initially, because resection of the gastrinoma rarely led to a cure, total gastrectomy was performed to normalize acid secretion. With the introduction of H2-histamine receptor antagonists and proton pump inhibitors (PPIs) (omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole), medical control became possible in all cases, but diagnosis became more complicated (11).

In the case of localized gastrinoma with ZES, PPI therapy (symptomatic treatment) is combined with surgical intervention. The high expression of somatostatin in gastrinomas makes them sensitive to somatostatin analog drugs, which are used as anti-proliferative agents in patients who are not candidates for surgical treatment. Surgical excision is typically recommended either for sporadic gastrinoma or for gastrinoma associated with MEN-1, if complete tumor removal is possible. The overall treatment algorithm proposed by R.E. Rossi et al. is shown in Figure 2 (8).

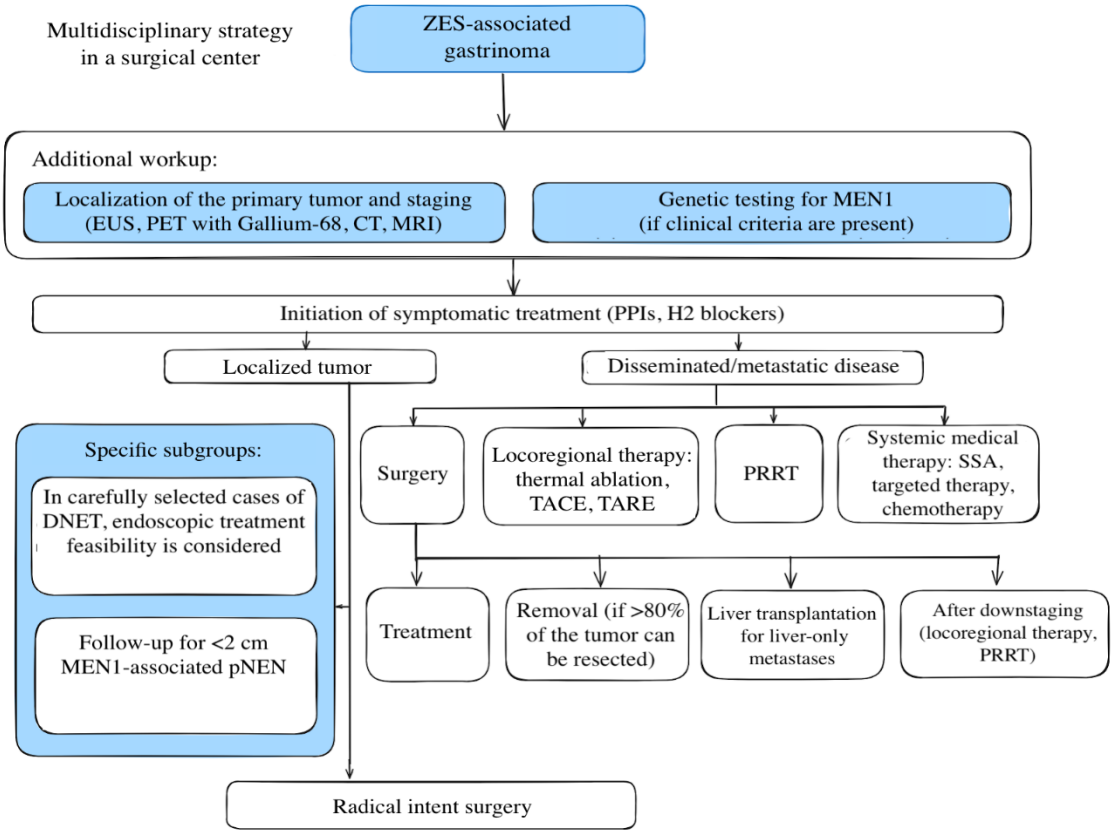

Figure 2. Treatment Algorithm for Zollinger-Ellison Syndrome (8) (TAE – Transarterial Chemioembolization, TARE – Transarterial Radioembolization, PRRT – Peptide Receptor Radionuclide Therapy, SSA – Somatostatin Analog, DNEO – Duodenal Neuroendocrine Tumor, PNEO – Pancreatic Neuroendocrine Tumor, OLT – Orthotopic Liver Transplantation)

This strategy ensures a high 20-year overall survival rate, reaching 48-83%. At the same time, the 20-year survival rate directly associated with ZES is 58-96% (30).

Surgical Strategy

Since most gastrinomas are located in the duodenum, are small in size, and are localized in the submucosal layer, they are difficult to detect. For this reason, the surgical approach, in the absence of preoperative visualization, includes a diagnostic search for the tumor. After a complete examination of the abdominal cavity, the duodenum and the head of the pancreas are mobilized using the Kocher maneuver and are then carefully palpated. Intraoperatively, ultrasound (US) examination is performed with a linear probe in the duodenum and pancreas to identify the primary tumor and metastases in the liver. The next step involves performing intraoperative endoscopy, advancing the probe into the duodenum. Gastrinomas may be detected here using transillumination of the intestinal wall as non-transilluminated spots. The identified lesion is marked with a suture, and the duodenum is opened around it for complete resection. If the tumor still cannot be found, a longitudinal incision of 3 cm is made on the anterior surface of the second part of the duodenum, and the entire wall of the intestine is palpated. Suspicious areas are excised with a full-thickness margin of normal tissue and sent to the pathology laboratory. After this, the intestine is closed transversely to reduce the likelihood of strictures. An experienced surgeon can identify 98% of lesions in patients with previously negative instrumental imaging results. Therefore, in cases of sporadic ZES, surgery should be performed as soon as possible, even with negative imaging results. Pancreatic gastrinomas are enucleated if they are located at least 3 mm away from the main pancreatic duct. If they are closer, the approach depends on the location of the lesion: in the head/neck or distal part (body, tail) of the pancreas. In the first case, pancreaticoduodenectomy is performed. In the second case, distal pancreatectomy with or without splenectomy is performed (8). Regional lymph nodes are typically removed to improve long-term surgical outcomes. In the publication by F. Giovinazzo et al., only 8% of patients who underwent radical resection developed a recurrence, compared to 100% of those who underwent enucleoresection. After radical resection, metastases to the lymph nodes were present in 82% of cases. The mean time to recurrence in patients with sporadic gastrinoma was 66.7 months in the enucleoresection group compared to 181.1 months in the radical resection group (p=0.007) (31). In the study by D.K. Bartsch et al., systematic lymphadenectomy (in patients with sporadic gastrinoma) involving the removal of more than 10 lymph nodes led to a higher biochemical cure rate compared to no lymphadenectomy or selective lymphadenectomy. Systematic lymphadenectomy was associated with increased survival rates in patients with a

follow-up period of 83 months. Negative prognostic factors for disease-related survival included pancreatic location (p=0.029), tumor size of 25 mm or more (p=0.003), Ki-67 proliferation index greater than 55% (p<0.001), preoperative gastrin level of 3000 pg/mL or higher (p=0.003), and liver metastases (p<0.001). Gender, age, type of surgery, and the presence of lymph node metastases did not affect disease-free survival or disease-related survival (32).

The participants of the 2016 Vienna Consensus Conference formulated the following statements regarding the treatment of gastrinomas:

- All patients with sporadic gastrinomas, without medical contraindications, should undergo surgical examination by a surgeon experienced in the treatment of gastrinomas.
- As part of any gastrinoma removal surgery, systematic removal of lymph nodes in the peritumoral area should be performed, which can be evaluated in terms of its prognostic value and the potential to increase the cure rate.
- A group of specialists, highly qualified in this type of surgery, should consider the possibility of surgical resection in patients with neuroendocrine tumors with preoperative vascular support.
- In patients with MEN1/ZES and pancreatic neuroendocrine tumors ≤2 cm or with neurofibromatosis-associated pancreatic neuroendocrine tumors, routine surgical exploration is not recommended based on imaging studies. In patients with pancreatic neuroendocrine tumors >2 cm, enucleation during surgery remains the generally recommended surgical procedure, while pancreaticoduodenectomy is reserved for specific, selected cases (6).

Although pancreaticoduodenectomy provides complete removal of regional lymph nodes and good recurrence-free survival, it is not recommended as a standard procedure due to the high postoperative morbidity and favorable prognosis for patients with small residual disease (33).

Embolization

Liver metastases or primary liver gastrinomas require a somewhat different approach. Surgical resection of a single liver metastasis, secondary to pancreatic tumors/MEN1, can be curative, and even in the case of multiple liver metastases, surgical resection is still possible. Hepatic transarterial chemoembolization is usually associated with surgical resection. In some cases, liver transplantation may be required (34). At the time of diagnosis, 25% of gastrinomas metastasize, typically to the liver. Although liver embolization reduces ZES, post-embolization syndrome (fever, malaise, abdominal pain) often develops. Embolization is performed via access through the right femoral artery (using polyvinyl alcohol particles, etc.). Embolization may target the right, left hepatic arteries, or both hepatic arteries, depending on the extent of metastasis. The result of embolization is tumor necrosis on CT (35). A rare case of a 55 mm hepatic gastrinoma in a 29-year-old male has been reported. Serum gastrin levels increased from 4620 pg/mL to 23,600 pg/mL within 20 seconds after the injection of calcium gluconate into the corresponding hepatic artery. Following percutaneous transhepatic portal vein embolization, an extended right hepatic lobectomy and cholecystectomy were performed. The patient's serum gastrin level on day 1 post-operation decreased to 65 pg/mL (36).

Antisecretory Therapy

Proton pump inhibitors (PPIs) suppress the gastric H+K+ ATPase, which is necessary for gastric acid secretion. PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, and others) are among the most widely used drugs worldwide. Most patients with ZES require lifelong treatment for severe gastric acid hypersecretion, and for them, PPIs are the drugs of choice. Treatment usually begins with PPI doses equivalent to 60 mg of omeprazole per day. However, systematic long-term use of PPIs can be associated with adverse health consequences, including renal pathology, increased incidence of lung and gastrointestinal infections, impaired absorption of nutrients (iron, calcium, magnesium, vitamins), and fundic gland polyps (37, 38). Treatment of ZES patients with PPIs should be accompanied by periodic monitoring of serum vitamin B12 levels, as hypochlorhydria and achlorhydria have been shown to decrease the absorption of this vitamin (39).

Since the primary gastrinoma is not always localized, in these cases, the main treatment may be related to conservative therapy. A case report by A. Aamar et al. described a 57-year-old woman suffering from diarrhea for 10 months. A liver biopsy revealed metastatic well-differentiated neuroendocrine tumor. The serum gastrin level was significantly elevated at 9100 pg/mL (normal <100 pg/mL). The chromogranin concentration in the serum was also elevated. Abdominal MRI, somatostatin receptor scintigraphy, and endoscopic ultrasound did not reveal a primary neuroendocrine tumor focus. Colonoscopy was normal. Esophagogastroduodenoscopy showed marked gastric folds and multiple duodenal ulcers consistent with ZES syndrome. The patient was prescribed high doses of omeprazole and octreotide. Diarrhea improved, and the serum gastrin level normalized within 4 weeks of treatment initiation (40).

In the mid-20th century, only complete gastrectomy was effective for controlling gastric acid secretion; however, with the advent of histamine H2 receptor antagonists (later PPIs), medical management became possible for nearly every patient with ZES. Before the introduction of PPIs, cimetidine, ranitidine, and famotidine were used to effectively control gastric acid. Comparative studies have shown that cimetidine, ranitidine, and famotidine have a relative efficacy ratio of 1:3:32 per 1 mg for inhibiting acid secretion in ZES. Famotidine has a longer duration of action (by 30%) compared to ranitidine and

cimetidine. High doses of these medications are prescribed to ZES patients. H2 receptor antagonists typically do not have pronounced side effects (41).

Antiproliferative Therapy

Inoperable cases of ZES, the presence of liver metastases, and lymph node involvement require the initiation of antiproliferative therapy. The tyrosine kinase inhibitor sunitinib has shown promising results in patients with advanced pancreatic neuroendocrine tumors. The median survival was 11.4 months compared to 5.5 months in the placebo group ($p<0.001$). At the end of the data collection, 9 deaths (10%) were recorded in the sunitinib group compared to 21 deaths (25%) in the placebo group (hazard ratio for death 0.41; 95% CI 0.19–0.89; p=0.02). Side effects associated with sunitinib included diarrhea, nausea, and vomiting (42).

The effect of everolimus in a clinical trial involving 410 patients was similar: the median progression-free survival was 10.0 months compared to 4.6 months for patients receiving placebo with advanced pancreatic neuroendocrine tumors. Drug-related side effects were predominantly grade 1 or 2 and included stomatitis (64% of patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23% vs. 6%), mainly in the upper respiratory tract. Anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%) were more frequently observed in the everolimus group than in the placebo group. The median duration of everolimus treatment was 2.3 times longer than that of placebo (38 weeks vs. 16 weeks) (43). It should be noted, however, that these studies were not specifically focused on the effects of these drugs in gastrinomas.

The combination of 5-fluorouracil, doxorubicin, and streptozocin resulted in a 39% response rate in patients with advanced pancreatic neuroendocrine tumors. This regimen was given to patients in anticipation of reducing the anatomical size of the tumor prior to resection. Tumor involvement with the major mesenteric artery and/or vein was observed in 19 (66%) and 24 (8%) patients, respectively, before treatment, and after therapy, persistent involvement with the artery and/or vein was observed in 17 (59%) and 22 (76%) patients. Despite the demonstrated effectiveness, significant stage reduction is rarely encountered (44).

The combination of capecitabine and temozolomide has demonstrated activity in the treatment of metastatic pancreatic neuroendocrine tumors, with response rates ranging from 30% to 70%, which was not associated with the expression of O(6)-methylguanine DNA methyltransferase and ALT (alternative lengthening of telomeres). In a clinical study, the median overall survival was 73.2 months, and the 5-year survival rate was 58.6% (45). In a multicenter, randomized Phase II study (n=133) involving patients with advanced low- and intermediate-grade pancreatic neuroendocrine tumors, progression-free survival was 22.7 months in the capecitabine/temozolomide group and 14.4 months in the temozolomide-only group. In the final analysis, the median overall survival was 53.8 months for temozolomide and 58.7 months for capecitabine/temozolomide (hazard ratio=0.82, p=0.42). O(6)-methylguanine DNA methyltransferase deficiency was associated with a response. The response rates to capecitabine/temozolomide treatment and median progression-free survival represent the highest recorded outcomes for pancreatic neuroendocrine tumors (46). The toxicity of this therapy is relatively low and includes anemia, neutropenia, thrombocytopenia, and headache (47).

Currently, targeted treatment methods such as antiangiogenic therapies, multitargeted kinase inhibition, and mTOR inhibition are actively being studied as new approaches to combat tumor progression in patients with metastatic lesions (48). Despite some advances, surgical treatment remains the primary approach for managing gastrinomas with ZES in the case of unresectable liver metastases, and orthotopic liver transplantation may be a relevant option (4).

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is a form of treatment for neuroendocrine tumors that express somatostatin receptors. This treatment involves the use of somatostatin analogs labeled with a radioactive marker. In samples of gastroenteropancreatic neuroendocrine tumors, somatostatin receptors sst2a were identified in 93% of cases (49). The most commonly used peptides for PRRT are DOTATOC and DOTATATE. Lutetium (Lu^{177}) is more frequently used than yttrium (Y^{90}) for labeling somatostatin analogs (SSAs) due to its lower renal toxicity and its application in scintigraphy and dosimetry (33). A randomized distribution of 229 patients with metastatic neuroendocrine tumors of the small intestine into the experimental group of 116 individuals (Lu-Dotatate + octreotide) and the control group of 113 patients (octreotide) showed significant benefits in the experimental group. The estimated progression-free survival rate at 20 months was 65.2% in the experimental group compared to 10.8% in the control group. Clinically significant myelosuppression was observed in less than 10% of patients in the experimental group (50). Other clinical trials have also confirmed the efficacy of PRRT agents (Lu-DOTATATE, Lu-DOTA-octreotate) in terms of progression-free survival, response to treatment, acceptable toxicity, and overall survival, particularly with Ki 67 ≤55% (51, 52).

4. CONCLUSION

Due to the complexity of diagnosing Zollinger-Ellison syndrome (ZES), clinicians should remain vigilant in cases of significant gastric acid hypersecretion, persistent gastroesophageal reflux disease (GERD), diarrhea, and abdominal pain.

Increasing awareness among healthcare providers about ZES will help reduce diagnostic delays and shorten the time to correct diagnosis. Even when ZES is suspected, one must always consider the possibility of multiple endocrine neoplasia type 1, one of the manifestations of which is ZES. This pathology may be indicated by hypercalcemia, the detection of hyperparathyroidism, and a family history of genetic predisposition to this group of diseases.

A review of the literature has shown that an effective diagnostic algorithm has been developed, which, when properly followed, leads to an accurate diagnosis. An essential step in the diagnostic process is the testing of serum gastrin levels and the measurement of gastric pH, and in some cases, secretin stimulation testing is added. When determining the nature of the disease, it is important to consider any antisecretory medications the patient may be taking, particularly proton pump inhibitors (PPIs), which significantly reduce gastric acidity (and increase pH). These medications should be discontinued at least one week prior to laboratory testing.

A major challenge can be determining the location of the tumor, especially if it is small in size. Instrumental imaging methods are not always effective. Even endoscopic ultrasound may miss gastrinomas, particularly in the small intestine. The high expression of somatostatin receptors in gastrinomas allows the use of somatostatin analogs in diagnostic procedures. It is advisable to include PET with gallium-68 and other similar methods in the diagnostic plan, as these can be useful not only for tumor detection but also for staging.

Despite the development of instrumental methods, in a significant number of cases, patients with Zollinger-Ellison syndrome (ZES) undergo surgical exploration for the tumor, although this method is not always successful. The surgical approaches to the treatment of gastrinomas have changed significantly since the mid-20th century, largely due to the advent of antisecretory therapy. Previously, the only way to reduce gastric acidity in patients with ZES, before the development of H2-receptor antagonists and proton pump inhibitors (PPIs), was total gastrectomy. Currently, long-term PPI therapy allows maintaining gastric pH at an acceptable level; however, there may be trends toward malabsorption of certain vitamins, macro-, and microelements. Surgical removal of the tumor is mandatory when it is localized. However, in advanced cases, when metastasis is present, surgical methods are supplemented with chemoembolization, peptide receptor radionuclide therapy (PRRT), and chemotherapy. In cases involving significant lymph node involvement, radical lymphadenectomy is required, which improves the chances of cure. In general, it can be stated that although complete cure is not achieved in many cases of ZES, overall survival and disease-free survival times have significantly improved with the introduction of new pharmaceutical regimens and treatment methods.

Conclusions:

1) Since Zollinger-Ellison syndrome is based on the hyperproduction of gastrin by the tumor, the mandatory diagnostic steps should include serum gastrin testing, gastric pH measurement, and tumor localization.

2) The study of the immunohistological characteristics of gastrinomas has led to the development of diagnostic and therapeutic methods based on the use of somatostatin analogs.

3) Surgical treatment of sporadic gastrinomas in ZES has a high success rate. However, in advanced cases with metastasis, surgery is complemented by vascular embolization, chemotherapy, and radiopharmaceutical therapy.

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