SYSTEMATIC REVIEW OF ZOLLINGER-ELLISON SYNDROME

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ABSTRACT

Zollinger-Ellison syndrome (ZES) or Strom-Zollinger-Ellison syndrome is a rare disorder which is triad of gastric acid hyper secretion, severe peptic ulceration, and non-beta cell islet tumour of pancreas (gastrinoma). The syndrome is often caused due to the tumour of the duodenum or pancreas producing increased levels of hormone gastrin which produces excess hydrochloric acid in the stomach leading to ulceration in almost 95% of patients. Gastrinomas may occur as single tumours or as multiple, small tumours. About one-half to two-thirds of single gastrinomas are malignant tumours that most commonly spread to the liver and lymph nodes near the pancreas and small bowel. Nearly 25 percent of patients with gastrinomas have multiple tumours as part of a condition called multiple endocrine neoplasia type I (MEN I) where the tumours are present in pituitary gland and parathyroid glands in addition to pancreas. The diagnosis of ZES has improved with development in biochemistry detection and advances in radiological imaging, angiography, Somatostatin receptor scintigraphy etc. The treatment of patients with Zollinger-Ellison syndrome (ZES) has undergone dramatic evolution during the past decade. Till 1970s, the only effective therapy for controlling acid hyper secretion was total gastrectomy. Currently, after the introduction of potent antisecretory drugs, such as H2 antagonists and proton pump inhibitors, chemotherapy, chemoembolisation etc has brought greater relief in the morbidity and complications related to ZES. In this article we have given an overview about the epidemiology, pathogenesis, clinical manifestations, advancement in diagnosis and management of ZES.

KEYWORDS: Zollinger-Ellison syndrome, gastrin, gastrinomas, Multiple Endocrine Neoplasia Type.
**INTRODUCTION**

Zollinger-Ellison syndrome (ZES) is caused by gastric acid hyper secretion characteristically resulting in severe gastroesophageal peptic ulcer disease, which is due to the ectopic secretion of gastrin, by a neuroendocrine tumour (gastrinoma), usually present in the duodenum or pancreas.\(^1\)\(^–\)\(^4\) Zollinger-Ellison syndrome is named after two surgeons at the Ohio State University, Robert M. Zollinger (1903-1992) and Edwin H. Ellison (1918-1970).\(^5\) The ZES, as described in 1955, is characterized by peptic ulcers of the upper gastrointestinal tract refractory to medical therapy, diarrhea and severe gastric acid hyper secretion associated with non-beta islet cell tumours of the pancreas.\(^6\) In the 1960s, gastrin was discovered as the key hormone in the pathogenesis of the gastric hyper secretion.\(^7\)

The signs and symptoms of ZES are primarily due to gastric acid hyper secretion. The most common initial symptom is abdominal pain and 90-95% of patients develop peptic ulcers in the upper gastrointestinal tract.\(^8\) With further advances in biochemical detection techniques, as well as improved understanding of the gastrointestinal hormone interactions, specifically the identification of the role of secretin stimulation on the serum gastrin levels.\(^9\) Advances in radiological imaging, angiography, and endoscopic techniques allowed for more precise tumour localization. Finally, understanding the natural history of the tumours responsible for ZES has allowed us to make evidence-based recommendations about their ultimate management.\(^10\)

**EPIDEMIOLOGY**

The early estimates of ZES incidence were most likely falsely low given large degree of overlap with peptic ulcer disease.\(^11\) Whereas the true incidence remains unknown, there is general consensus that approximately 0.1–3 persons per million develop gastrinoma each year in most geographical areas.\(^12,\)\(^13\) Patients represent the entire adult age span, from the second to the eighth decades of life. There is a slight preponderance of males among reported cases, and the distribution of the syndrome is worldwide. Patients represent all socioeconomic groups, and no particular racial, ethnic, religious, or cultural associations have been reported.\(^14\)

**SYMPTOMS\(^{15,16}\)**

The signs and symptoms of ZES are primarily due to gastric acid hyper secretion. The most common initial symptom is abdominal pain. Other symptoms are

- Diarrhea.
- Burning, aching, gnawing or discomfort in upper abdomen.
- Acid reflux and heartburn.
- Nausea and vomiting.
- Bleeding in digestive tract.
- Unintended weight loss.
- Decreased appetite.
- Steatorrhea.

**CAUSES**

The gastrinoma is a gastrin-cell, or G-cell, adenoma or adenocarcinoma. It is histologically characteristic of islet cell tumours in general, with a uniform cuboidal pattern of cells with prominent nucleoli, modest cytoplasm, and few mitotic figures in either benign or malignant tumours. These tumours are usually malignant (60%), multifocal (60%), and may reside in the pancreas (70% to 90%), duodenal wall (15% to 20%), or in extraintestinal locations (5% to 15%) such as lymphatic tissue or the liver. More than 90% of gastrinomas occur within the gastrinoma triangle, which is bounded by the third portion of the duodenum, the neck of the pancreas, and the porta hepatis. Pancreatic gastrinomas may be prominent, obvious lesions, but more frequently they are small (0.5 to 2.0 cm), multiple, intrapancreatic lesions. Duodenal gastrinomas are usually small intramural lesions that may be more prominent on either the mucosal or serosal side of the bowel wall. Careful attention at endoscopy to the inner wall of the air-distended duodenum is important to detect small, mucosally oriented duodenal lesions. Although single or multiple discrete adenomas or adenocarcinomas are most common, diffuse hyperplasia of G cells throughout the pancreatic islets has also been described in association with this syndrome. The presence of seeming lymphatic or hepatic "primaries" of gastrinoma has always been a troubling finding, and this unusual but consistent finding in a small number of cases has been suggested to represent isolated metastatic foci from a previously resected tumours. Because many patients have undergone previous gastric or duodenal operations, the inadvertent previous removal of a duodenal gastrinoma is a theoretical possibility in these cases. The vast majority of gastrinomas are found in isolated, sporadic cases without other genetic association. Between 10% and 25% of gastrinomas appear as part of the Multiple Endocrine Neoplasia-Type I (MEN-I) Syndrome, and are associated with parathyroid, pituitary, and other pancreatic apudomas. A small number of gastrinomas appear to be familial, without MEN-I manifestations, and a number of isolated gastrinoma kindred have been identified.
DIAGNOSIS

Blood tests
The majority of patients with ZES demonstrate fasting basal hypergastrinemia. Normal gastrin values vary from laboratory to laboratory, but basal gastrin levels less than 50 pg/mL (25 pM) are not likely to be associated with ZES. Basal gastrin levels between 100 and 1000 pg/mL are considered intermediate, and fasting levels greater than 1000 pg/mL are virtually diagnostic of the disease.\[^{25}\]

A reliable test is the measurement of basal acid secretion (BAO) or, alternatively, it can be useful to determine the pH of the gastric juice which can be obtained during endoscopy or through a nasogastric tube. If the gastric pH is >2 in the absence of antisecretory therapy, the patient is hypochlorhydric and therefore, ZES can be excluded; if the pH is <2 and the plasma gastrin is higher than 1 000 pg/mL, the diagnosis of ZES is certain while, if the pH is <2 and the plasma gastrin concentration is between 100 and 1 000 pg/mL, a secretin test must be carried out.\[^{26}\]

The secretin test is performed by the administration of 2 IU/kg of secretin intravenously in 2 min, after having taken a blood sample in order to perform the basal gastrin concentration; after the injection, blood samples are taken after 2.5, 5, 10, 15 and 30 min. An increase of plasma gastrin >200 pg/mL is diagnostic of ZES. The test can give a false positive result in some patients with Type A chronic atrophic gastritis, but this is identified by measuring the gastric pH.\[^{27}\] The secretin test can also give a false negative result in 10% of patients with ZES, and this is usually associated with a malignant course of the disease.\[^{28}\]

The calcium test might be of value in those patients in whom ZES is strongly suspected when the secretin test is negative. There is agreement in the literature that calcium and meal tests are less useful than secretin for detecting ZES.

Imaging techniques
To localize and stage gastrinomas, conventional non-invasive and occasionally invasive diagnostic modalities may be required.

1. Somatostatin receptor scintigraphy[SRS]
At present, the most important study should be somatostatin receptor scintigraphy (SRS) using 111 In-pentetreotide with single photon emission tomography (SPECT) scanning.\[^{29}\]
Recent studies demonstrated that SRS allows total body localization study simultaneously at one time, thus allowing detection of liver and distant metastases and it is more sensitive in both localizing the primary gastrinoma and identifying patients with liver metastases than conventional methods such as CT, MRI, US.\textsuperscript{[30]}

2. Ultrasonography
Ultrasonography can detect gastrinomas in 30% of cases and the detection rates are better for lesions greater than 3 cm in diameter and are poor for lesions smaller than 1 cm.\textsuperscript{[31]}

3. Endoscopic ultrasonography [EUS]
Using EUS, the sensitivities as high as 79-82\% can be obtained.\textsuperscript{[32,33]} A recent prospective study found a sensitivity of 93\% and a specificity of 95\% in the localization of intrapancreatic lesions.\textsuperscript{[34]} EUS, in combination with SRS up to 69\%, although it may still miss up to 50\% of duodenal gastrinomas.\textsuperscript{[35]} Therefore, when a gastrinoma is suspected, endoscopy or EUS should also be performed to identify duodenal as well as pancreatic gastrinomas, especially when multiple lesions are suspected as in MEN 1.\textsuperscript{[36,37]}

4. Magnetic resonance imaging and computed tomography
A comparative study demonstrated that MRI is equivalent to dynamic CT. Furthermore, MRI is considered the most sensitive technique for demonstrating liver and bone metastases in patients with neuroendocrine tumours and is recommended for monitoring the response to therapy. However, CT and MRI are both very sensitive and specific methods for demonstrating hepatic metastases and pancreatic tumours, and they show specific advantages in routine tumour staging and monitoring of therapy.\textsuperscript{[38,39]}

5. Angiography
Functional studies, measuring hormonal gradients by transhepatic portal venous sampling, seem to be more sensitive; however, this method is invasive, and does not lead to the exact location and requires considerable expertise. A modification of the hormonal gradient during angiography has been developed; in brief, secretin is injected intra-arterially selectively into different vessels and hepatic venous samplings are collected and assayed for hormonal gradients. Selective angiography can identify the site of the tumour in up to 75\% of cases, but has largely been supplanted by the combination of Octreoscan, EUS and CT.\textsuperscript{[40,41]}
In about 20% of patients, a gastrinoma cannot be identified by conventional imaging techniques and SRS.\textsuperscript{[42]} In these cases, during laparotomy, operative techniques such as duodenal transillumination and intraoperative ultrasound can be used.\textsuperscript{[43]}

![Diagnostic algorithm for Zollinger-Ellison Syndrome](image)

**TREATMENT**

The immediate and sustained control of gastric acid hyper secretion and surgical resection of tumours are the most important aspects of disease management in patients with Zollinger-Ellison syndrome.\textsuperscript{[44]} The rapid initiation of treatment with adequate dose of anti secretory drugs is therefore a priority in patients with suspected Zollinger-Ellison syndrome.\textsuperscript{[45]}

**Medical management**

- Anti secretory drugs
  1. **Proton pump inhibitors**

Proton pump inhibitors are the first choice of treatment in Zollinger- Ellison syndrome. PPIs are highly effective antisecretory agents that are well tolerated and have few long-term negative side effects even with chronic use at high doses.\textsuperscript{[46]} The PPIs commonly used are omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole.\textsuperscript{[47]}

It works by binding to $\text{H}^+\text{K}^+\text{ATPase}$ at the luminal aspect of the gastric parietal cell, thus interfering with both basal and stimulated gastric acid secretion. Most patients require doses that are slightly higher than those necessary for patients with idiopathic PUD; however, many
can achieve acceptable outcomes with daily dosing because of the long duration of action of these drugs.\[48\] Parenteral drug treatment is necessary in case oral therapy is not tolerated in case of vomiting or in cases where ZES first suspected in the postoperative period after surgery in complications of ulcer diseases.\[45\] PPIs have been proven to be safe and effective in the maintenance therapy of patients with ZES for more than 10 years, without any effect of related toxicity.\[49\]

- **Omeprazole**
  Omeprazole has been most widely used in the treatment of ZES.

  Gastric acid hyper secretion is usually controlled with < 80mg/day but dosage up to and even exceeding 200mg/day have been used in some patients.\[45\]

- **Lanzoprazole**
  Lansoprazole is an efficacious, well-tolerated antisecretory agent in patients with Zollinger-Ellison syndrome.\[50\]

  Dosage of 60 mg/day will control acid output in most patients and 60 mg every 12 hours will control acid output in all. Doses can then often be slowly and progressively reduced.\[44,50\]

2. **H\textsubscript{2}-antagonist**

   H\textsubscript{2}-antagonist like cimetidine, ranitidine, famotidine are used in the treatment of ZES.\[51\]

- **Ranitidine**
  Ranitidine is the drug of choice among the H2 antagonists, due to its low side effects and its limited interaction with other drugs. However, despite the first excellent results, long-term studies have shown that the use of these drugs is limited by many factors such as poor control of the gastric acid hyper secretion and sometimes the need for high and frequent doses of the drug.\[52\]

  Acid secretion can be controlled acutely in 70% of patients with an infusion of ranitidine 1 mg/kg/h, while 4 mg/kg/h will control acid in all.\[44\]
• **Somatostatin analogs**

It is well-known that somatostatin and its analogs are able to reduce gastric acid and serum gastrin levels in patients with ZES, with both short-term and long-term administration.\(^\text{[53]}\) In addition to immediate-release subcutaneous octreotide, other long-acting somatostatin analogs such as lanreotide, which can be administered every 10-14 d, and octreotide LAR, which can be administered every 28 d, are currently available on the market.\(^\text{[54,55]}\)

**Surgery**

Surgery plays a key role in the treatment of Zollinger-Ellison syndrome because the ZES-related deaths were due to tumour spread; none were due to hypersecretory complications.\(^\text{[56,57]}\) Patients with the Zollinger–Ellison syndrome who do not have multiple endocrine neoplasia type 1 or metastatic disease should be offered surgical exploration for possible cure. Initially, the surgical therapy proposed was total gastrectomy with the aim of removing the high levels of gastrin from the target organ.\(^\text{[59]}\); in the past 20 years, improved pharmacological control of gastric acid hypersecretion has eliminated the role of surgery in containing the hypersecretion itself. The availability of PPIs allows us to adequately control the symptoms in all patients with ZES, making the natural history of gastrinomas, the only determining factor in long-term survival.\(^\text{[60]}\) The indications for surgery in patients with ZES-MEN 1 are controversial, since previous experience has shown that surgery rarely cures these patients.\(^\text{[61,62]}\)

**Chemotherapy**

Therapeutic strategies for the management of patients with metastatic gastroenteropancreatic endocrine tumours have to take into consideration the fact that controlling the hormone-mediated symptoms often improves the quality of life, to the point that the patients feel well despite the extensive metastatic disease.\(^\text{[63]}\) At best, chemotherapy has furnished only unclear results utilizing the classical anti-tumoral agents, such as 5-fluorouracil, in controlling metastatic endocrine tumours. Systemic chemotherapy reached a new therapeutic dimension immediately after the introduction of streptozotocin (STZ) into clinical use.\(^\text{[64]}\)

**Interferon**

The validity of interferon has been sustained in neuroendocrine tumors, especially in the carcinoid syndrome. Gastrinomas can be treated with chemotherapy and/or interferon when they grow and metastasize.\(^\text{[65]}\)
Chemoembolization or embolization

Chemoembolization, which uses a combination of gelfoam and chemotherapeutic agents (streptozotocin or doxorubicin), may determine a notable improvement in the quality of life of the patient and is usually accompanied by a reduction in circulating peptide serum levels and the size of the tumour.\cite{65}

Figure 2: Therapeutic algorithm of Zollinger-Ellison Syndrome. PPI: proton pump inhibitors; SST: somatostatin analogs; IFN: interferon.

CONCLUSION

ZES is disease of increased acid secretion due to gastrinomas which causes severe ulceration in duodenum and pancreas. Often patients exhibited with severe abdominal pain and secondly diarrhoea. Diagnosis should be prompted by high index of suspicion based on clinical presentation, and confirmatory biochemical testing should be performed and imaging techniques can be used to localize and stage gastrinomas. Recent developments in surgical techniques, and pre-and intra-operative imaging investigation, have permitted the identification and successive resection of more than 95% of gastrinomas. Therefore all localized gastrinomas should be excised, if possible. Treatment with antisecretory drugs can reduce the complications and morbidity. Proton pump inhibitors have been proven to be safe and effective, without particular side effects over a long period of time. Chemotherapy and chemoembolisation places a greater role in treating metastatic tumours. Somatostatin analogs also reduce gastric acid hypersecretion, serum gastrin and gastric ECL-cells, thus
contributing to curing the disease more effectively. Finally with multidisciplinary approach a greater contribution can be brought in the treatment of patients with ZES.

REFERENCES


