International Journal of Advance and Applied Research
www.ijaar.co.in
ISSN – 2347-7075 Impact Factor – 7.328
Peer Reviewed Bi-Monthly
Vol.4 No.29 July-Aug 2023

An Update on Zollinger-Ellison Syndrome

Boddula Mahathi[1], Dr. Syeda Nishat Fathima[2]
[1,2]Department of Pharmacology, Jayamukhi College of Pharmacy, Narsampet, Warangal-506332, Telangana, India
Corresponding Author- Boddula Mahathi
Email- mahathiboddula@gmail.com

Abstract:
Zollinger-Ellison syndrome is a rare disease, characterized by the presence of acid hypersecretion, gastric-duodenal ulcer disease, and a gastrin-secreting pancreatic or extrapancreatic tumor with difficult primary location. The therapy is initially long-term medical to reduce exposure to acid (high-dose proton pump inhibitors) and surgical treatment. The present article highlights the etiology, pathophysiology, diagnosis, treatment and prognosis of Zollinger-Ellison syndrome.

Keywords: Zollinger-Ellison syndrome; diagnosis; treatment

Introduction:
Zollinger-Ellison syndrome is a rare condition in which one or more tumors grow in the pancreas or in the upper part of the small intestine. The tumors are called gastrinomas. These gastrinomas produce large amounts of the hormone gastrin. Gastrin causes the stomach to produce too much acid, which leads to peptic ulcers. High gastrin levels also can cause diarrhea, belly pain and other symptoms. Zollinger-Ellison syndrome is slightly more common in men than in women. [1]

Classification:
Gastrinomas represent one of the most common pancreatic endocrine tumors. A smaller percentage of gastrin-secreting tumors (20-40%) originate from the duodenum. Seventy-five percent of gastrinomas occur sporadically, and the remainder are associated with multiple endocrine neoplasia type 1 (MEN 1) syndrome. Sporadic tumors are usually solitary and malignant. MEN 1-associated tumors are typically multiple, but they may be more localized at the time of diagnosis. Fifty to sixty percent of gastrinomas are malignant, based on the presence of metastases at the time of diagnosis. Nevertheless, gastrin-secreting tumors are often slow growing and associated with prolonged survival, despite complications originating from intestinal ulcerations. [2]

Epidemiology:
Zollinger-Ellison Syndrome (ZES) is a rare condition, with an estimated incidence of 0.1-0.5 cases per million people per year. The condition affects both men and women equally, with the average age of onset in the fourth or fifth decade of life. The mean age of onset of ZES is 43 years; however, patients with multiple endocrine neoplasia-type 1 and ZES (MEN 1/ZES) present a decade earlier. Generally, a 5- to 7-year delay in diagnosis occurs. In a prospective study, fewer than 3% of patients were younger than 20 years, whereas 7% were older than 60 years at the time of disease onset. [3]

Etiology:
Zollinger-Ellison syndrome (ZES) is caused by a non–beta islet cell, gastrin-secreting tumor of the pancreas that stimulates the acid-secreting cells of the stomach to maximal activity, with consequent gastrointestinal mucosal ulceration. In most individuals with ZES, the condition appears to occur spontaneously for unknown reasons (sporadically). However, in approximately 25 percent of affected individuals, ZES occurs in association with the genetic syndrome known as multiple endocrine neoplasia type 1 (MEN-1). In most patients, MEN-1 is inherited as an autosomal dominant genetic condition. MEN-1 is caused by changes (mutations) in the *MEN1* gene. The *MEN1* gene regulates production of a protein that appears to play some role in

preventing tumor development (tumor suppressor). [4]

Pathophysiology:

The symptoms of Zollinger-Ellison syndrome (ZES) are secondary to hypergastrinemia, which causes hypertrophy of the gastric mucosa, leading to increased numbers of parietal cells and increased maximal acid output. Gastrin by itself also stimulates acid secretion, resulting in increased basal acid secretion. The large quantity of acid produced leads to gastrointestinal mucosal ulceration. It also leads to diarrhea and malabsorption. Usually, gastric acid secretion is controlled by negative feedback mechanisms by somatostatin released by gastric D cells to maintain gastric acid homeostasis and maintain proper gastric pH. However, due to unopposed gastrin release by the neuroendocrine tumor, gastrinoma results in severe PUD because of excess gastric acid secretion to the post-bulbar regions of the duodenum from the esophagus via the trophic effect of gastrin on enterochromaffin-like and parietal cells.

Gastrin works on the parietal cells of the gastric glands, causing them to secrete more hydrogen ions into the stomach lumen. In addition, gastrin acts as a trophic factor for parietal cells, causing parietal cell hyperplasia. Normally, hydrogen ion secretion is controlled by a negative feedback loop by gastric cells to maintain a suitable pH, however, the neuroendocrine tumor that is present in individuals with Zollinger–Ellison Syndrome has no regulation, resulting in excessively large amounts of secretion. Thus, there is an increase in the number of acid-secreting cells, and each of these cells produces acid at a higher rate. The increase in acidity contributes to the development of peptic ulcers in the stomach, duodenum (first portion of the small bowel) and occasionally the jejunum (second portion of the small bowel), the last of which is an 'atypical' ulcer. [5]

Clinical Manifestations:

Abdominal pain is the most common symptom, present in 75% of patients. Typically, it is located in the upper abdomen and mimics that of peptic ulcer disease. This symptom is reported more frequently by men and patients with the sporadic form of ZES. Of patients with ZES, 73% have diarrhea; this is the most common symptom in patients who have multiple endocrine neoplasia-type 1 and ZES (MEN 1/ZES) as well as in female patients. The combination of diarrhea and abdominal pain is present in more than half the patients. Heartburn is the third most common symptom, and this symptom mimics gastroesophageal reflux disease (GERD). Other symptoms include nausea, vomiting, gastrointestinal bleeding, and weight loss. Gastrointestinal bleeding frequently is due to ulceration in the duodenum and is the presenting symptom in 25% of patients. In patients in whom MEN 1/ZES is suspected, a history indicative of nephrolithiasis, hypercalcemia, and pituitary disorders should be sought. A family history of nephrolithiasis, hyperparathyroidism, and gastrinoma also may be present. [6]

Diagnosis:

Diagnosis of ZES is first suspected on the basis of the clinical manifestations. Elevated fasting serum gastrin (FSG) levels are almost invariably present. FSG levels 10 times higher than normal and a gastric pH of <2 confirm the diagnosis. If the FSG level is elevated less than 10 fold and the gastric pH is <2, secretin stimulation (abnormal: increase >120 pg/ML) and basal acid (abnormal: >15 mEq/hr-basal) tests need to be done. Imaging studies (somatostatin receptor scintigraphy, CT scan, abdominal or endoscopic ultrasound) are required to localize the gastrinoma.

Esophagogastroduodenoscopy may be indicated to detect duodenal ulcerations. [7]

Differential Diagnosis:

Differential diagnoses include other causes of increased acid output and elevated FSG levels: Helicobacter pylori infections, retained gastric antrum, gastric outlet obstruction, renal failure, antral G cell syndromes, idiopathic gastroesophageal reflux or peptic ulcer disease, and physiological causes of hypergastrinemia (atrophic gastritis, pernicious anemia, or use of potent antisecretory drugs). [8]

Complications:

Zollinger-Ellison Syndrome (ZES) can lead to several complications if left untreated. [9] These complications include:

1. **Gastrointestinal bleeding:** Ulcers caused by ZES can lead to gastrointestinal bleeding, which may manifest as vomiting blood, passing dark stools, or developing anemia.
2. **Obstruction:** Large ulcers or scarring in the small intestine can cause obstruction,

leading to symptoms such as nausea, vomiting, and abdominal pain.

3. **Perforation:** Ulcers caused by ZES can penetrate the wall of the stomach or small intestine, leading to a perforation or a hole in the organ. This can cause severe abdominal pain, fever, and signs of infection, and requires immediate medical attention.
4. **Malabsorption:** Excessive acid production can damage the lining of the small intestine, leading to malabsorption of nutrients such as fats, proteins, and vitamins.
5. **Carcinoid tumors:** In rare cases, ZES can lead to the development of carcinoid tumors, which are slow-growing tumors that can spread to other parts of the body.
6. **Other endocrine tumors:** ZES can be associated with other endocrine tumors, such as insulinomas (tumors that produce insulin) or glucagonomas (tumors that produce glucagon).

Treatment:

In patients with ZES, the two main principal therapeutic objectives are to control the gastric acid hypersecretion which causes the most debilitating symptoms (ulcers, diarrhea and dehydration) and to control the growth of the tumor which, even if slow-growing, is able to produce early and diffuse hepatic metastases.

Proton pump inhibitors have been used to more drastically inhibit gastrin action on the parietal cells, thus allowing the patient to rapidly return to a normal clinical condition without the need for surgery. If it is possible to eliminate the morbidity and mortality caused by acid hypersecretion, the majority of patients affected by ZES should be able to be maintained in good clinical condition, without symptoms. In ZES, antisecretory drugs have been proven to be safe and effective, without particular side effects over a long period of time, even 15 years or more. The dose of PPIs such as oral omeprazole and intravenous pantoprazole must be adjusted to normalize basal acid output levels to less than 15 mEq per hour and less than 5 mEq per hour for those with prior surgery to decrease acid secretion. Eighty milligrams of pantoprazole by mouth twice daily is the typical dose. Several studies have shown that treatment with somatostatin analogs has an inhibiting effect on tumoral growth in patients with malignant gastrointestinal neuroendocrine neoplasias, such as pancreatic tumors or carcinoids, and is able to stabilize the tumoral growth in 37-80% of patients; in only a few patients (0-17%), a reduction of the tumor dimensions has been observed. [10]

The surgical treatment of gastrinomas has evolved from total gastrectomy to specific tumour surgery. Its main objective is to achieve cure or control of the tumour, and to prevent its spread and metastasis. Even with all the diagnostic technology currently available, the preoperative localization of gastrinomas does not reach 100% of the cases and, for this reason, only adequate surgical exploration has the potential to localize 100% of the tumours. It has been estimated that approximately 60-90% of all gastrinomas are malignant. Tumour progression and the development of metastases are the main determining factors for survival. Consequently, surgery alone offers the patient a 31-50 chance of cure. Routine surgical exploration has been shown and established to increase long-term survival. Indications for surgery in sporadic Zollinger-Ellison syndrome All patients with a laboratory diagnosis of sporadic Zollinger-Ellison syndrome have an indication for surgical exploration because up to 30% of gastrinomas are not diagnosed by radiological studies. Although most gastrinomas grow very slowly, 60-90% are malignant, and of these, 25% grow very quickly. The incidence of lymphatic metastases in duodenal gastrinomas has been reported in up to 40% of cases; pancreatic gastrinomas have hepatic metastases more frequently. It should be noted that up to 15% of gastrinomas not identified on radiological studies are also not identified during surgical exploration. Surgery can achieve definitive cure of gastrinoma in 51–60% of cases in the immediate postoperative period, in 40% of cases at 5 years, and in 34% of cases 10 years postoperatively [11]

Prognosis:

Because gastrinoma is a component of Zollinger-Ellison syndrome, the prognosis-based cancer stage must be considered. 90% to 60% of gastrinomas are malignant and can spread to the liver, lymph nodes, or other distant organs. The incidence of pancreatic gastrinomas is 50%, and the incidence of duodenal gastrinomas is 10% in the liver. Since pancreatic gastrinomas have a worse

long-term survival rate than duodenal gastrinomas, liver metastasis directly impacts overall survival. The patients without liver metastases had a 95% 20-year survival rate, which is an important discovery. The patients with liver metastases had a 15% 10-year survival after the surgery. However, there was no evidence that lymph node involvement reduced survival in the absence of liver metastases.

Conclusion:

In conclusion, the future prospects for the treatment of Zollinger-Ellison Syndrome are promising, with the development of targeted therapies, immunotherapy, and gene therapy showing great potential. As research in these areas continues to advance, it is hoped that more effective and targeted treatments will be developed, improving the quality of life for individuals living with this condition.

References:

1. Rossi, R. E., Elvevi, A., Citterio, D., Coppa, J., Invernizzi, P., Mazzaferro, V., & Massironi, S. (2021). Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies. World journal of gastroenterology, 27(35), 5890–5907. https://doi.org/10.3748/wjg.v27.i35.5890
2. Connors, J. M. (2007). Zollinger-Ellison Syndrome. In xPharm: The Comprehensive Pharmacology Reference. https://doi.org/10.1016/b978-008055232-3.60707-x
3. Pipeleers-Marichal, M., Somers, G., Willems, G., Foulis, A., Imrie, C., Bishop, A. E., Polak, J. M., Häcki, W. H., Stamm, B., Heitz, P. U., & Klöppel, G. (1990). Gastrinomas in the Duodenums of Patients with Multiple Endocrine Neoplasia Type 1 and the Zollinger-Ellison Syndrome. The New England Journal of Medicine, 322(11), 723–727. https://doi.org/10.1056/nejm199003153221103
4. National Organization for Rare Disorders. (2023, March 11). Zollinger-Ellison Syndrome - Symptoms, Causes, Treatment | NORD. https://rarediseases.org/rare-diseases/zollinger-ellison-syndrome/
5. Pisegna J. R. (1999). The effect of Zollinger-Ellison syndrome and neuropeptide-secreting tumors on the stomach. Current gastroenterology reports, 1(6), 511–517. https://doi.org/10.1007/s11894-999-0012-8
6. Gibril, F., & Jensen, R. T. (2004). Zollinger-Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion. *Current gastroenterology reports*, *6*(6), 454–463. https://doi.org/10.1007/s11894-004-0067-5
7. Deveney, C. W., & Deveney, K. E. (1987). Zollinger-Ellison Syndrome (Gastrinoma): Current Diagnosis and Treatment. Surgical Clinics of North America, 67(2), 411–422. https://doi.org/10.1016/s0039-6109(16)44192-7
8. Arnold R. (2007). Diagnosis and differential diagnosis of hypergastrinemia. Wiener klinische Wochenschrift, 119(19-20), 564–569. https://doi.org/10.1007/s00508-007-0878-0
9. Roy, P. K., Venzon, D. J., Shojamanesh, H., Abou-Saif, A., Peghini, P., Doppman, J. L., Gibril, F., & Jensen, R. T. (2000). Zollinger-Ellison syndrome. Clinical presentation in 261 patients. Medicine, 79(6), 379–411. https://doi.org/10.1097/00005792-200011000-00004
10. Verdugo, M. a. C., Soto, R. M. R., Salgado, D. L. N., Medrano, M. E. B., & León, W. A. (2022). Clinical and Surgical Management of Zollinger-Ellison Syndrome: A Literature Review. *International Journal of Medical Science and Clinical Research Studies*, *02*(12). https://doi.org/10.47191/ijmscrs/v2-i12-27
11. Krampitz, G. W., & Norton, J. A. (2013). Current management of the Zollinger-Ellison syndrome. Advances in surgery, 47, 59–79. https://doi.org/10.1016/j.yasu.2013.02.004
12. Yu, F., Venzon, D. J., Serrano, J., Goebel, S. U., Doppman, J. L., Gibril, F., & Jensen, R. T. (1999). Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 17(2), 615–630. https://doi.org/10.1200/JCO.1999.17.2.615