Review Article

Zollinger-Ellison syndrome: A Comprehensive Guide on Diagnosis and treatment.

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ABSTRACT

Zollinger-Ellison syndrome (ZES) is a rare condition characterized by the formation/growth of one or more tumors known as gastrinomas in the upper portion of small intestine or pancreas or duodenum. The syndrome causes the overproduction of gastrin, which can result in severe peptic ulcers, uncontrollably high stomach acid secretion, and potentially dangerous side effects such gastrointestinal bleeding and perforation. In 1955 Robert M. Zollinger and Edwin H. Elliaon from Ohio State University published a report on two patients who had pancreatic islet cell tumors with severe ulcer diathesis. The ulcerogenic turnout syndrome was first introduced by Zollinger and Ellison, despite the fact that a few such instances had been previously documented. Because symptoms are nonspecific and gastrin levels can fluctuate, diagnosis is frequently difficult. Serum gastrin tests, stomach acid measurement to verify acid hypersecretion, and imaging methods including CT, MRI, and somatostatin receptor scintigraphy (SRS) to pinpoint the location of gastrinomas are important diagnostic tools. Complications including perforations and gastrointestinal bleeding. The main goals of ZES management are to reduce acid hypersecretion by employing high-dose proton pump inhibitors (PPIs) and, when practical, surgically removing gastrinomas. The degree of tumors spread and the effectiveness of therapy interventions determine long-term results. ZES is a problem since it can recur and can convert malignantly, even with advances in medicinal and surgical therapy.

Key words: Gastrinomas, gastrin, Zollinger, Ellison, pancreatic islet tumors, proton pump inhibitors**.**

1. Introduction

Zollinger-Ellison syndrome is a type of Gl tract disorder caused by pancreatic or duodenal gastrinoma and hypersecretion of gastric acid, which usually results in peptic ulcer recurrence, persistent diarrhoea, and gastro-oesophageal reflux syndrome[1]. The patient with Zollinger-Ellison syndrome gastric PH level less than 2 and 1000pg/mL of gastrin hormone level. The patient with Zollinger-Ellison syndrome, Survival rate is based on if the tumors or cancerous and if they spreadable[2].

For patient who had a successful surgical treatment, the ten years survival rate is 90%. The ten years survival rate is 25% in cases where surgery is either is not feasible or not curative[3].

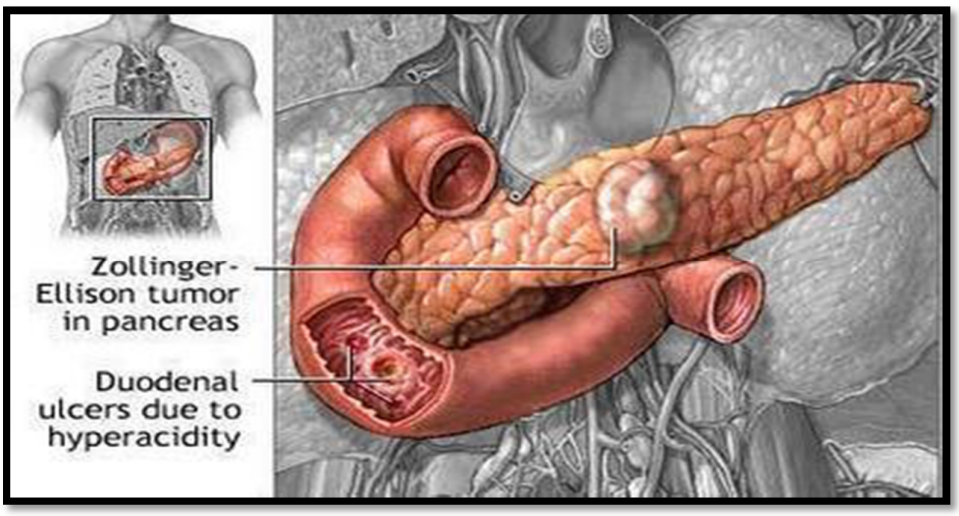


Fig:1Anatomical location of a pancreatic Zollinger-Ellison gastinoma.

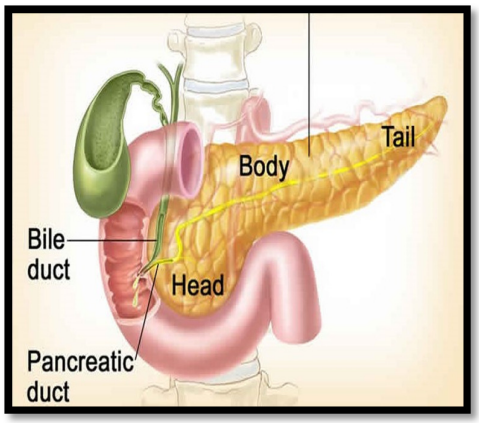
1.1. History

In 1955 Robert M. Zollinger and Edwin H. Elliaon from Ohio State University published a report on two patients who had pancreatic islet cell tumors with severe ulcer diathesis[4].The ulcerogenic turnout syndrome was first introduced by Zollinger and Ellison, despite the fact that a few such instances had been previously documented[4]. Dr. Zollinger and Ellison first recognized the illness that would eventually carry their names in 1955. The two discussed the instances of two young ladies who had perforated jejunal ulcers. Severe gastric hypersecretion was present in both cases. Dr. Zollinger and Dr. Ellison hypothesized that a hormone released by these tumors was generating the stomach acid output that resulted in peptic ulcer syndrome [4].In 1960, Dr. Roderic Gregory and Dr. Hilda Tracy isolated a gastrin-like material from a Zollinger-Ellison syndrome patient's pancreas, identifying gastrin as the hormone responsible for the disease. [5]

Fig: 2 Dr. Robert Milton Zollinger and Dr. Edwin Homer Ellison

1.2 Etiology

Zollinger-Ellison syndrome (ZES) symptoms are nonspecific and might be associated with those of other gastrointestinal illnesses [(1)]. One is, Zollinger-Ellison syndrome (ZES) is caused by tumors knowns as gastinomas. Tumors induce an excessive discharge of stomach acid. Extra acid can develop painful peptic ulcers within the lining of your stomach acid intestine [(2)].Second one is, approximately 25% of those with gastrinoms have them as a result of multiple endocrine neoplasia (MEN 1). They may also have tumors in the pancreas or other organs, which is leads to Zollinger-Ellison syndrome [(2)].



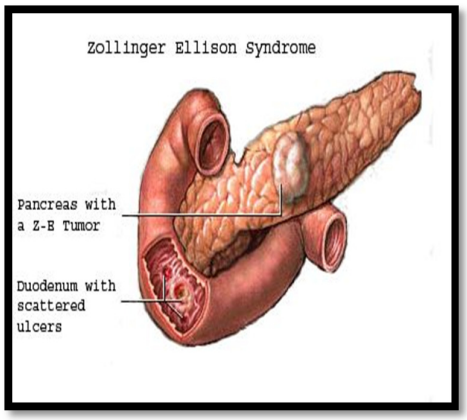


Fig: 3 Normal **Fig: 4 Affected**

1.3 Pathophysiology

Gastrinomas (Gastrin-Secreting Tumors): Gastrinomas are typically found in the duodenum (70-90% of cases) or pancreas (10-30% of cases). These tumors are often small but can be multiple and malignant in a significant proportion of cases[(6,7,8)].

Autonomous Gastrin Secretion: Gastrinomas secrete gastrin autonomously, meaning they are not subject to the usual feedback inhibition mechanisms that regulate gastrin release in response to stomach acid levels[(6,7,8)].

Excessive Gastric Acid Secretion: The increased levels of gastrin result in excessive gastric acid production by parietal cells in the stomach. This acid hypersecretion leads to a state of hyperchlorhydria, where there is an abnormally high concentration of acid in the stomach[6,7,8].

Peptic Ulcer Formation: The combination of hypergastrinemia and hyperchlorhydria predisposes individuals with ZES to develop multiple, recurrent, and refractory peptic ulcers. These ulcers can occur in the stomach and duodenum and are characterized by their resistance to conventional ulcer therapy due to the ongoing acid secretion[6,7,8].

1.4 Signs and Symptoms of ZES [1, 9, 10],

GERD,

Gastric ulcer,

Nausea,

Vomiting,

weight loss,

chronic diarrhea

abdominal pain,

severe heart burn,

intestinal bleeding,

esophagitis,

liver metastasis.

1.5 Complications

Acid secretions can cause bleeding and perforation of GI tract, including the oesophagus, stomach, and duodenum[11].

Significance risk include motility as a result of surgery to remove gastrinoma or other malignancies from MEN1[11].

2. Diagnosis

1. Medical history
2. Family history
3. Blood test
4. Imaging and ultra sound endoscopy
    - Contrast-enhanced computed tomography (CT) scan
    - Contrast enhanced magnetic resonance imaging (MRI)
    - Somatostatin receptor scintigraphy (Octreoscan)
    - Somatostatin receptor positron emission tomography
    - Endoscopic ultrasound
5. Secretin provocative test

1. Medical history:

Reviewing medical history and symptoms of patient [12].

2. Family history:

A genetic variant associated with type I Multiple Endocrine Neoplasia (MEN I). About one-third of MEN I patients get ZES at some point during the course of their illness. Hyperparathyroidism, pancreatic islet cell tumors, and pituitary tumors with varying degrees of penetrance are the hallmarks of MEN I (Wermer's syndrome). Consequently, it is advised that all patients undergo a comprehensive ZES evaluation as part of the MEN I evaluation [13].

3. Blood test

Serum gastrin levels are tested after fasting. High concentrations (often >1000 pg/mL) are indicative of ZES. Prior to testing, it's critical to make sure the patient has been off proton pump inhibitors (PPIs) for the appropriate amount of time, as PPIs might raise salivary levels [1].

4.Imaging and ultra sound endoscopy

When ZES is associated gastrinoma is suspected, the initial diagnostic step is to localize the main tumor and its metastases [1].

Contrast-enhanced computed tomography (CT) scan: Using contrast-enhanced computed tomography (CT) scans can help find liver metastases, pancreatic head tumors, and original tumors bigger than 1 cm [1].They are 95% to 98% specific and 59% to 78% sensitive. In contrast, sensitivity falls at extra-pancreatic sites and tumor sizes smaller than 1 cm [1].

Contrast-enhanced magnetic resonance imaging (MRI): Magnetic resonance imaging (MRI) with contrast enhancement has shown a high specificity (i.e., 100%) in identifying liver metastases and small pancreatic tumors, but a subpar sensitivity ranging from 25% to 85%. Notably, compared to a CT scan, an MRI demonstrated a better sensitivity for the identification of liver metastases [1].

Somatostatin receptor scintigraphy (Octreoscan): Gastrinomas have been localized using somatostatin receptor scintigraphy (Octreoscan). In this assay, octreotides labeled with indium radioactivity are administered. Octreotide binds specifically to somatostatin receptors on gastrinoma cells. For the identification of primary tumors and their metastases, it demonstrated strong specificity (93%–94%) and sensitivity (between 77% and 78%), while sensitivity drops for tiny tumors (< 1 cm). Somatostatin receptor scintigraphy (Octreoscan) can be used in conjunction with single-photon emission CT (SRS-SPECT) to increase diagnostic accuracy. Compared to Octreoscan alone, several studies demonstrated improved primary tumor detection sensitivity and specificity, at 78%–88% and 97%, respectively [1]

Somotostatin receptor positron emission tomography: Somatostatin receptor positron emission tomography (PET) approaches have demonstrated significant promise in the last several years for the detection of distant metastases, especially bone lesions, and for better localizing gastrinomas and other NENs. Peptides that attach to somatostatin receptors, which are widely distributed on the NEN surface, can be ligated to the radioisotope 68Ga. In comparison to the previously described diagnostic approaches, this method demonstrated greater specificity and sensitivity (72%–100% and 83%–100%) for localizing the primary tumor, particularly small tumors [1].

Endoscopic ultrasound**:** Endoscopic ultrasound (EUS) has emerged as a crucial diagnostic technique for the localization of gastrinomas, especially those that are tiny (less than 2 cm). For pancreatic tumors, EUS has a sensitivity and specificity of 75%–100% and 95%, respectively. Unfortunately, in cases of duodenal localization, its sensitivity drops considerably, from 38% to 63%. One additional benefit of this method is the ability to confirm the diagnosis of NEN by performing a fine needle aspiration/biopsy (FNA/B) on cytologic and/or histologic materials. It has been claimed that EUS is a more accurate way to find tiny tumors than a CT scan [1].

5. Secretin provocative test

The secretin provocative test, which is used to diagnose ZES, is used in disputed instances[1]. These cases include patients who have gastric pH values less than 2, but whose fasting serum gastrin levels are below the upper range of normal. Before secretin is infused intravenously (IV), and again 2-, 5-, and 10-minutes following infusion, fasting gastrin levels are measured in order to conduct a secretin stimulation test. In response to secretin infusion, patients with gastrinomas produce excessively more gastrin. The direct expression of secretin receptors on the gastrinoma cell surface helps to explain this mechanism in part. Various thresholds for positive testing have been suggested, such as a 50% rise in gastrin concentration or an absolute increase of ≥ 110 pg/mL or ≥ 200 pg/mL. [1] In contrast, prior research indicated that a positive secretin-provocative test (≥ 120 pg/mL rise) would have 100% specificity and 94% sensitivity, respectively. The research reports that between 6% and 20% of patients may experience a false-negative response [1].

4. Treatment

The two main goals of treatment for ZES patients are to reduce the hypersecretion of gastric acid, which results in the most incapacitating symptoms (ulcers, diarrhea, and dehydration), and to slow the growth of the tumor, which can cause early and widespread hepatic metastases even though it is growing slowly [2].

1) Anti-secretary agents
2) Control of hormonal secretion
3) Control of neoplasia
4) Control of tumor size

1)Anti-Secretary Agent

If ZES is suspected, it is crucial to avoid potential consequences while awaiting the definitive results of the diagnostic testing. It is therefore recommended to begin antisecretory therapy as soon as possible, as it is generally well tolerated and does not have any specific contraindications [2].

a) Proton pump inhibitors such as

Omeprazole,

Esomeprazole,

Lanzoprazole,

Pantoprazole,

Rabeprazole.

b)Histamine H2 receptor antagonist

Cimetidine,

Ranitidine,

Femotidine.

a) Proton Pump Inhibitors

In Zollinger-Ellison Syndrome (ZES), proton pump inhibitors (PPIs) play a crucial role in the management of symptoms and complications associated with the disease [14].

Mechanism Of Action

PPIs irreversibly bind to and inhibit the hydrogen-potassium ATPase pump on the luminal surface of the parietal cell membrane, effectively blocking the release of stomach acid [1].

Common Adverse Effects

Headache, rash, dizziness, nausea, abdominal pain, flatulence, constipation, diarrhea [7].

Vitamin B 12

Reduced serum levels of vitamin B12, but not folate, have occasionally been reported during long-term proton pump inhibitor treatment[2].

This behavior appears to be connected to the drug's induction of achlorhydria, which is uncommon when using PPIs[2].

b)Histamine H2 receptor antagonist

H2 receptor antagonists are a useful therapy option for Zollinger-Ellison syndrome (ZES), although because of the condition's severity and complexity, they are typically not the first choice[15].

Example:

Cimetide

Ranitine

Famotidine

Mechanism Of Action

By reversibly binding to the histamine H2 receptors on the stomach parietal cells and preventing the endogenous ligand histamine from binding and acting, H2RAs reduce the amount of gastric acid secreted. H2 blockers are antagonists that compete with one another [17, 17, 18].

Advers Effects

Headache, lethargy, sleepiness, stomach ache, constipation, or diarrhea, impaired liver function, impaired renal function, hallucinations, delirium, disorientation, or slurred speech [16,17,18].

2) Control of Hormonal Secretion

Example:

Octreotide [(1)],

Lanreotide [(1)].

Mechanism Of Action

An equivalent of somatostatin is the synthetic polypeptide lanreotide, Turning on G-Proteins, Adenylate Cyclase inhibition, decrease in the levels of Camp, Hormone Secretion Reduction [(19)].

Adverse Effect

Nausea, Vomiting, Diarrhea, Abdominal Pain, Cramping, Hyperglycemia, Hypoglycemia, Pain or Discomfort in stomach, Cholelithiasis (Gallstones), Bradycardia, Malabsorption, Fatigue and HairLoss [(19)].

3) Control Of Neoplasia

Surgery

Between 1955 and the present, the function of surgery in the management of ZES has changed significantly. At first, a total gastrectomy was suggested as a surgical treatment to eliminate the target organ's elevated gastrin levels[(20)].

Even if treating neoplastic diseases with chemotherapy is difficult, all individuals can have their symptoms completely eliminated with appropriate medical therapy. However, more recently, some other reports have indicated that a highly effective way to prevent hepatic metastases has been the surgical excision of a gastrinoma. Currently, the main tumor is identified, removed, and liver metastases are prevented primarily through surgical exploration. Surgery's primary goals are to regulate the acid hypersecretion syndrome, remove the malignant tumor to increase survival, and stage the tumor. Given that the majority of ZES patients have either localized or occult illness upon presentation[(2)].

Methods

Due to the increased risk of radicality, pancreaticoduodenectomy offers total removal of the pancreatic head's regional lymph nodes, with superior disease-free survival (DFS) compared to enucleation. Laparoscopy is insufficient in these cases, and a laparotomy is required. Using imaging tools, the surgeon must locate and remove the non-localized lesion laparotomically. During surgery, techniques like palpation, ultrasonography, and duodenal wall transillumination can also help find gastrinomas in the pancreas and duodenum, as well as any lymph nodes or metastases in the liver[(1)].

Additionally, it has been claimed that after surgery, over 50% of patients are disease-free, and most of them stay that way for the next five to ten years[(2)].

It is crucial to keep in mind that the duodenum is the site of a significant portion of primary occult tumors. Because gastrinomas frequently metastasize in the lymph nodes and can occasionally originate here, it is crucial to remove all lymph nodes in the peripancreatic region, even if they don't seem enlarged. [(1)]Since nearly half of patients have nodal metastases, regional lymph nodes should always be resected [(2)].

4) Control Of Tumor Size

Systemic Chemotherapy

The antineoplastic drug Streptozotocin's dosage and administration schedule have been standardized by several studies, which have also recommended combining it with other cytotoxic medications like doxorubicin (Adriamycin) and 5-fluorouracil (5-FU). This combination of STZ and doxorubicin has proven to be more effective than other regimens, primarily STZ and 5-FU, and appears to be linked to a 69% objective response that lasts for 18 months and a median overall survival of 2.2 years. [(1)]

Interferon

Interferon has shown to be effective in treating neuroendocrine tumors, particularly those associated with carcinoid syndrome, in recent years. The literature's data show that interferon-alpha therapy stabilises tumors in 20–40% of patients with various gastrointestinal neuroendocrine tumors, including those that have metastasized gastrinomas. However, this therapy did not improve these patients' chances of survival. Therefore, it has been suggested that as gastrinomas spread and expand, they can be treated with interferon and/or chemotherapy. [(2)]

Conclusion

In conclusion, Zollinger-Ellison Syndrome (ZES) is a rare disorder marked by gastrin-secreting tumors, or gastrinomas, that cause excessive gastric acid production and severe peptic ulcers. Diagnosis involves measuring elevated gastrin levels and utilizing imaging techniques to locate the tumors. Effective management requires a combination of potent acid suppression with proton pump inhibitors and targeted treatment of gastrinomas through surgical or medical means. Despite its challenges, advancements in diagnostic and therapeutic strategies have improved patient outcomes. A multidisciplinary approach, involving gastroenterologists, endocrinologists, and surgeons, is essential for optimal care. Continued research and clinical developments offer promise for better understanding and managing this complex syndrome, ultimately enhancing patient quality of life.

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