Zollinger-Ellison Syndrome — Presentation, Diagnosis, Therapy

Zollinger-Ellison syndrome is one of the rare conditions that affect the duodenum or the pancreas. Tumors (gastrinomas) form in the duodenum or the pancreas, which secrete huge amounts of gastrin leading to excess acid production in the stomach. This excess acid results in the formation of related symptoms as well as peptic ulcers.

Definition and Background of Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome results from a **pancreatic tumor** in the **non-beta islet cells**, which stimulates the maximal activity of the **gastric acid-secreting cells**, resulting in **gastrointestinal ulceration** of the mucosa. **Multiple endocrine neoplasia type 1 (MEN 1)** is a familial autosomal dominant syndrome that includes Zollinger-Ellison syndrome as part of it; however, Zollinger-Ellison syndrome may still occur sporadically.

The primary tumor is located in the **pancreas, abdominal lymph nodes**, and the **duodenum**; however, it may be found in other **ectopic places** such as in the **ovaries, gall bladder, kidney, liver**, and **heart**.
Pathophysiology of Zollinger-Ellison Syndrome

In Zollinger-Ellison syndrome, there is **hypertrophy** of the **stomach mucosa** caused by **hypergastrinemia**, which increases the number of the **parietal cells** and the **maximal output of acid**. Acid secretion is also stimulated by gastrin leading to increased secretion of basal acid. Different complications may result from increased acid such as **ulcerations** of the gastrointestinal mucosa, **malabsorption**, and **diarrhea**. Malabsorption is caused by many factors such as hypersecretion of gastric acid, inactivated pancreatic enzymes and precipitation of bile salts.

Epidemiology of Zollinger-Ellison Syndrome

About 75% of cases have sporadic incidence while 25% cases are associated with multiple endocrine neoplasia (MEN) 1, that is characterized by pituitary tumors, hyperparathyroidism, and pancreatic endocrine tumors.

Spread of Zollinger-Ellison syndrome in the United States

About **0.1 % to 1 %** of patients suffering from duodenal ulcers in the United States have Zollinger-Ellison syndrome. And it is reported to have a **similar frequency as insulinoma**.

Spread of Zollinger-Ellison syndrome Globally

The incidence **differs from one country to another**, for example in Ireland it is reported as **0.5** cases per a million patients per year. In Sweden, the incidence is higher up to **1-3** cases per a million patients per year.

Dependence of the Zollinger-Ellison syndrome on gender, age and race

There is **no difference based on race**, and it appears that all races may be equally affected. **Males have a slightly higher risk** of developing the syndrome with a **1.3:1** male to female ratio. Zollinger-Ellison syndrome rarely appears in very young or old ages, with the **mean age of onset being 43 years**.

Presentation of Zollinger-Ellison Syndrome

History
The diagnosis of Zollinger-Ellison syndrome is based on a patient’s **history, physical examination, and a high index of clinical awareness**. Main symptoms include:

- **Abdominal pain**: It is the **most common symptom** presenting in more than 75% of the patients. The abdominal pain is usually located in the **upper abdominal region** and resembles the pain felt in **peptic ulcer disease**.
- **Diarrhea**: It is a common symptom too, with approximately 73% of the patients reporting it. In women, diarrhea is more common as a symptom than abdominal pain. It is also more common in patients suffering from Multiple endocrine neoplasia type 1 than sporadic cases of Zollinger-Ellison syndrome.
- **Heartburn**: It resembles the pain felt with gastroesophageal reflux disease.

Other less common symptoms include:

- Nausea
- Vomiting
- Gastrointestinal bleeding
- Weight loss

If there is a history of **hypercalcemia**, **pituitary disorders**, and **nephrolithiasis**, then **Multiple endocrine neoplasia type 1** should be suspected.

### Physical examination

Physical examination **may be normal** and not reveal any signs or findings. However, signs may be present and they include:

- Epigastric tenderness
- Jaundice, if there is a compression over the common bile duct due to the tumor
- Paleness due to the gastrointestinal bleeding
- Dental erosions
- Hepatomegaly, which suggests metastasis to the liver
Differential Diagnosis of Zollinger-Ellison Syndrome

Clinical pictures similar to Zollinger-Ellison syndrome

- Retained gastric antrum syndrome
- Antral G-cell hyperplasia
- Gastric outlet obstruction

Diagnosis of Zollinger-Ellison Syndrome

Laboratory studies

- **Fasting serum gastrin:** This is the **best screening test** for Zollinger-Ellison syndrome. Serial measurements of fasting serum gastrin should be performed on different days because of the fluctuation that happens to the gastrin levels from day to day.
- **Gastric acid secretary tests:** Zollinger-Ellison syndrome is suspected if the **basal acid output** is greater than 15 mEq/h. Zollinger-Ellison syndrome is also suggested in the case of a large gastric volume and a **gastric pH of less than 2.0**.
- **Serum calcium levels:** MEN type 1 is suspected in cases with high serum levels of calcium.

Imaging studies

- **Computed tomography scanning (CT):** Even though a CT scan is **not highly sensitive** for the localization of a primary tumor (it has 50% sensitivity), it can still be used to **localize some tumors** especially if the tumor is bigger than 1 cm and to evaluate metastatic diseases.
- **Somatostatin receptor scintigraphy:** It is the **imaging study of choice** for the detection of Zollinger-Ellison syndrome and is the **most sensitive** imaging modality for the detection of both primary and metastatic tumors.
- **Endoscopic ultrasonography:** It is still a new method used to localize gastrinomas.
- Abdominal ultrasound and **magnetic resonance images** can also be used; however, they have **lower sensitivity** than somatostatin receptor scintigraphy and CT scans.

Procedures

- **Esophagogastroduodenoscopy:** This procedure is used to look for **gastric folds hypertrophy** and **duodenal ulcerations**.

Management of Zollinger-Ellison Syndrome

Medical treatment

Surgical treatment of the tumor is the main therapy. However, medical treatment is used first to **control the gastric acid hypersecretion**; once it is controlled, imaging studies should be used to determine the size and location of the tumor in order to resect it.
Proton pump inhibitors are the main medications used in the control of gastric acid hypersecretion. Histamine 2 receptor blockers can also be used; however, proton pump inhibitors are superior. Interferon, octreotide, and chemotherapy may be used in the management of patients with metastatic disease. Hepatic metastasis may be treated by liver transplantation.

Surgical intervention

The main treatment for the tumor in Zollinger-Ellison syndrome is surgical resection especially in patients with no surgical contraindications and no metastasis. Surgical resection decreases the risk of developing hepatic metastasis. In cases of MEN type 1, surgical intervention rarely cures the condition; however, the risk of metastatic disease is decreased.

Follow up with secretin test, serum fasting gastrin levels, and somatostatin receptor scintigraphy after surgical resection is mandatory in order to make sure there is no recurrence. A follow-up evaluation should be done every year with the first one being after 3 to 6 months after surgical resection.

Proton pump inhibitors may be continued after surgical resection.

Complications

Some common complications are:

- Abdominal perforation as a sequel of ulceration.
- Gastric outlet obstruction.
- Esophageal atresia secondary to gastric acid reflux.
- Gastric carcinoids.
- Gastrointestinal bleeding.
- Bowel obstruction.

Prognosis

- Morbidity and mortality due to ZES are low because of improved management. Less than 5% of cases develop complications.
- Prognosis is good in ZES without associated metastatic disease.

Review Questions

The correct answers can be found below the references.

1. A 43-year-old woman presents to your office complaining of abdominal pain between meals and frequent diarrhea. You perform an endoscopy, and a duodenal ulcer distal to the duodenal bulb is revealed. A pancreatic mass is observed in a CT scan and a malignant islet cell tumor is revealed following a subsequent pancreatic tissue biopsy. What hormone would you expect to be highly elevated in this patient?

   A. Secretin
   B. Motilin
C. Gastrin
D. Vasoactive intestinal peptide
E. Cholecystokinin

2. A 46-year-old man presents to the emergency department with sudden severe upper abdominal pain. Physical examination reveals that he is febrile, tachycardic and hypotensive. He has a history of chronic lower back pain and recurrent nephrolithiasis. Emergency exploratory laparotomy is performed and a perforated gastric ulcer is revealed. The patient dies despite appropriate management. Multiple ulcers in the duodenum, jejunum, and stomach are revealed later by an autopsy. During the last few months he has been complaining of diarrhea and abdominal pain; however, he was not taking any medications except for ibuprofen for his lower back pain during the past three weeks. Which of the following is the most likely cause of the presentation of this man?

A. Cytomegalovirus infection
B. Chronic NSAID use
C. Gastrin-secreting tumor of the pancreas
D. Infection with H. pylori
E. Pancreatic tumor secreting vasoactive intestinal peptide

3. A 53-year-old male patient presented to your office complaining of persistent epigastric pain, which is preventing him from eating normally and caused him to lose 15 pounds over the last month. His past history includes a pituitary tumor status post-trans-sphenoidal resection and parathyroid neoplasia. By physical examination, you find out that there is tenderness over the epigastric region. What would you suspect based on the additional diagnostic tests?

A. Elevated levels of gastrin and decreased levels of fasting serum gastrin after administration of secretin
B. Normal levels of gastrin and normal levels of fasting serum gastrin after administration of secretin
C. Elevated levels of gastrin and elevated levels of fasting serum gastrin after administration of secretin
D. Decreased levels of gastrin and decreased levels of fasting serum gastrin after administration of secretin
E. Decreased levels of gastrin and elevated levels of fasting serum gastrin after administration of secretin

References


What Is Zollinger-Ellison Syndrome?. WebMD.

Zollinger-Ellison syndrome. MAYO CLINIC.

Correct answers: 1C, 2C, 3C

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