Popular Article

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" Zollinger-Ellison syndrome in dogs "

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Introduction

Zollinger-Ellison syndrome is a rare disorder caused by a tumor called a gastrinoma. The tumor secretes the hormone gastrin, which causes excess production of gastric acid, leading to severe recurrent ulcers of the esophagus, stomach, duodenum, and jejunum. The syndrome is characterized by severe peptic ulcer disease caused by gastrin-secreting neuroendocrine tumors, most commonly located in the **duodenum and pancreas**. Frequently gastrinomas are not recognized at initial clinical presentation and are often mistreated. Symptoms that should raise suspicion of a gastrinoma include idiopathic peptic ulcer disease or long-standing refractory diarrhea. The term gastrinoma is interchangeably used with ZES.

Zollinger-Ellison syndrome is caused by a **neuroendocrine tumor of the pancreas** that secretes gastrin, causing massive gastric acid secretion. In dogs, gastrinomas have been reported to arise from **non-beta pancreatic islet cells** (Hoenerhoff *et al.,* 2004).

Gastrinoma, a neuroendocrine tumor, which is uncommonly reported is basically responsible for the Zollinger-Ellison syndrome. This syndrome is characterized by hypersecretion of gastric acid, ulceration of upper GIT (gastrointestinal tract) and tumors of non-beta islet cell. **It was 1st reported in a dog in the year 1976**, and mostly domestic dogs, a few cats, and now a Mexican gray wolf have been reported to have this illness (Struthers *et al.*, 2018).

Anatomy, Pathophysiology, and Molecular Biology

Gastrin is a small peptide hormone that is produced by gastric and proximal duodenal G cells. Gastrin has trophic effects on the gastric mucosa and shows its action via cholecystokinin-2 (CCK) receptor to stimulate gastric acid secretion. If serum gastrin level elevates more than three to ten times the upper end of reference range, it has been suggested that measuring serum gastrin

may be helpful for diagnosing gastrinomas in dogs. Since gastrin clearance is predominantly renal, disorders like chronic kidney disease, hypercalcemia, the use of drugs like gastric acid-suppressants, meals, and long-distance racing can also have an impact on serum gastrin concentrations (Heilmann *et al.*, 2017).

Excessive secretion of gastrin leads to **hyperplasia of the crypt cells of the antral gastric mucosa** and **hyperstimulation of gastric acid production** from the parietal cells of stomach. Antral hyperplasia may result in gastric outflow obstruction. The excessive secretion of gastric acid leads to gastro-duodenal ulceration and oesophagitis due to gastro-oesophageal reflux (Gal *et al.,* 2011). In severe cases of the disease, deep gastric ulcers may erode blood vessels causing haemorrhage or perforate, causing septic peritonitis.

Gastrinomas have often metastasized to local lymph nodes or to the liver at the time of diagnosis. Gastrinomas have only ever been reported in a very few dogs and cats and the disease is extremely rare.

Signalment and clinical signs

Gastrinomas are uncommon. They occur in **middle aged dogs** (average 8.2 years, 3.5-12 years). Cats are reported to suffer from gastrinoma ranged in age from 10-12 years. There is no breed predilection. **Females** may be at slightly greater risk (Gal *et al.,* 2011).

Vomiting and weight loss are the clinical signs frequently recorded. Lethargy, depression, inappetence to anorexia, and intermittent diarrhoea are also commonly reported. Less frequent signs include melena, polydipsia, abdominal pain, hematochezia, haematemesis, and obstipation (Struthers *et al.*, 2018).

Physical examination findings may include abdominal pain, fever, tachycardia, pale mucus membrane and dehydration in extremely sick animals due to severe GI ulceration or perforation.

Clinical signs result from gastrin-induced hypersecretion of gastric acid and hyperplasia of gastric mucosa.

Diarrhoea and steatorrhoea are caused by large amount of acidic fluid entering the duodenum and jejunum and by the elevated circulating levels of gastrin that reduce intestinal water and ion absorption (Ward, 2010).

Diagnosis

Although ZES is uncommon, a patient should be immediately evaluated if they have refractory peptic ulcer disease, persistent diarrhoea, absence of *H. pylori* infection, or if their

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condition has not improved despite *H. pylori* medication and acid suppression therapy.

CBC may reveal a regenerative anemia (due to GI bleeding), leukocytosis and neutrophilia with or without left shift.

Biochemical abnormalities include hypoalbuminemia, hypoproteinemia, **hypokalemia, hypochloremia, hyponatremia, metabolic alkalosis,** hyperbilirubinemia and mild increase in serum liver enzyme activities.

Contrast enhanced radiographic studies may show evidence of gastroduodenal ulceration, prominent gastric rugal folds, thickened pyloric antrum or rapid small bowel transit time.

Abdominal ultrasound may reveal gastric ulcer, thickened gastric wall or pylorus or evidence of metastasis in liver or regional lymph node.

Endoscopic findings include esophageal inflammation or ulceration, thickened gastric rugae, excessive fluid in stomach, hypertrophied pyloric antrum and duodenal ulceration.

Basal gastric acid secretion : This test is commonly performed in humans and is abnormally increased in more than 80% of human with gastrinoma. In dogs gastric pH will be very low 0.99-1.5 (<3) (Ettinger *et al.,* 2005).

Basal gastrin concentration in serum: It is best screening test for gastrinoma in humans. Other disease syndromes associated with increased basal serum gastrin concentration include kidney failure, chronic gastritis, gastric outflow obstruction, liver diseases, drugs like H2 blockers, proton pump inhibitors, glucocorticoid. In humans with gastrinoma, its concentration >1000 ng/L combined with gastric pH <2.5 is diagnostic for gastrinoma without further testing. Dogs with confirmed gastrinomas typically have serum gastrin concentrations greater than 3 times (often 10–200 times) the upper limit of the reference interval (Hughes, 2006; Ward, 2010). **Baseline serum gastrin concentration** in dogs varies among reports, probably because of different assays, and ranges from **10 to 40 ng/L,** 66 to76 pg/mL, 23 to 104 pg/mL, **20 to 100 pg/mL**, 27 to 85 pg/mL, 45 to 98 pg/mL, or as a mean of 40 pg/mL or 71 pg/mL (Struthers *et al.*, 2018).

Secretin stimulation: Secretin stimulates gastrin secretion in patients with gastrinoma but not in healthy individuals. In dogs, serum samples should be collected before and 2, 5, 10 and 30 minutes following I/V administration of 2-4 U/kg of secretin.

Calcium stimulation: Calcium infusion stimulates a rise in serum gastrin concentrations only if there is gastrinoma. Calcium is administered as an intravenous bolus of 2mg/kg over 1 minute. Serum samples are collected before and 15, 30, 60, 90 and 120 minutes after calcium administration (Ettinger *et al.*, 2005).

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Medical Therapy

1. **Surgical resection or reduction of gastrinoma and/or metastases**
2. Medical control of gastrin secretion from the tumor cells
3. Adjunct medical therapy includes treatment of gastric acid hypersecretion, GI ulceration and fluid and electrolyte losses.

The tumor should be excised if possible. Medical therapy should precede attempts to excise the tumor to decrease the clinical signs and ulcer formation. It's been suggested that if there is a favorable response to medical therapy preoperatively, only tumor excision need be done. However, if the animal is refractory to medical management, surgical intervention should include tumor removal and total gastrectomy to remove the target organ. Also, a selective vagotomy should be done if no tumor is found or if metastasis is present (Shaw, 1988).

Somatostatin analogues: Somatostatin inhibits gastrin and hydrogen ion secretion in gastrinomas and in gastric parietal cells. Octreotide @ 2-8 µg/kg SC bid or tid for 10-14 months.

Gastric hyperacidity: Agents used to control gastric hyperacidity include H2 receptor antagonist such as cimetidine (5-10 mg/kg PO, SC, IV, q6h or q8h), ranitidine (1-2 mg/kg PO, SC, IV q8h or q12h), famotidine and proton pump inhibitors like omeprazole (0.7 mg/kg PO q24h), pantoprazole.

Gastrointestinal ulceration: Treatment include surgical resection, control of gastric hyperacidity and cytoprotective agents such as sucralfate (1 g q8h for large dogs, 0.5 g q8h for smaller dogs), misoprostol (2-5 µg/kg PO q8-12h) (Ettinger *et al*., 2005).

Prognosis

The prognosis for canine patients with gastrinoma is guarded to poor, primarily due to metastasis to the liver and local lymph nodes which already has taken place in 85% of cases at the time of diagnosis.

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