Canine Insulinoma

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Introduction

Canine insulinomas are uncommon insulin-secreting pancreatic beta-cell tumors. Insulinomas are usually solitary and discrete masses, but multiple tumors and diffuse infiltrates have also been reported.[14] These tumors can occur in either limb or the body of the pancreas with no predilection for one location. Insulinomas are malignant in nature with 95% or more developing metastasis. [14] The most common sites of metastasis include the liver, regional lymph nodes, and peripancreatic omentum; pulmonary metastasis is rare. [14] Hypoglycemia is the cause of clinical signs, which can include weakness, seizures, muscle fasciculations, nervousness, collapsing episodes, tremors, ataxia, and disorientation. Signs are usually intermittent and can be triggered by exercise, fasting, excitement, or eating. Treatment of acute hypoglycemia should be undertaken at presentation by administering IV dextrose. Long-term treatment of choice is surgery to remove the primary pancreatic tumor and any visible metastases. Medical management including dietary modification, minimizing exercise and stress, glucocorticoids and additional therapies such as diazoxide, octreotide, and streptozotocin is used if surgery is not an option for the owner or when signs recur after surgery. Due to the malignant nature of insulinomas, long-term prognosis is guarded to poor. Patients that undergo both surgery and medical management have longer disease free intervals and survival times, with median survival times of up to 2 years. [14]

History and Presentation

Insulinomas are seen most commonly in middle-aged to older dogs. They have been more commonly reported in large breed dogs such as Golden Retrievers and Labrador Retrievers but can be seen in any size dog. [14] There is no sex predisposition. Clinical signs are caused by hypoglycemia and an increase in circulating catecholamine concentrations and include weakness,

seizures, collapsing episodes, tremors, ataxia, and disorientation. Polyphagia, weight gain, and peripheral polyneuropathies have also been reported.[1, 14, 19, 22] Signs are often gradual in onset and can be variable in their progression.[8] They are usually episodic in nature and may be triggered by exercise, fasting, excitement, or eating. Dogs with chronic hypoglycemia can tolerate low blood glucose concentrations (i.e., 20 to 30 mg/dL) for prolonged periods without clinical signs, and only small additional changes in the blood glucose concentration are then required to produce symptomatic episodes. [14] These dogs are usually symptomatic for 1 to 3 months prior to being seen by a veterinarian. [14] Physical exam findings in these patients are usually unremarkable, but weakness, lethargy, weight gain, or rarely a peripheral neuropathy may be present on examination.

Pathophysiology (Include Anatomical Considerations)

Insulinomas are functional tumors arising from the beta cells of the pancreatic islets. The beta cells are associated with the endocrine portion of the pancreas and are responsible for the secretion of insulin in response to an increase in blood glucose. A continuous supply of glucose is essential to brain function. Therefore, in normal patients, euglycemia is maintained by intricate interactions between the endocrine system, the autonomic nervous system, and the liver. Glucose movement in and out of circulation and glucose utilization by tissues are regulated by the peripheral glucose-lowering hormone insulin and the glucose-raising hormones glucagon, cortisol, growth hormone, and epinephrine. When blood glucose rises above normal limits, insulin secretion increases and lowers the blood glucose back to normal range. Similarly, when the blood glucose drops below normal range, the synthesis and secretion of insulin decreases. When the blood glucose drops below 60 mg/dl, the counterregulatory hormones, glucagon and epinephrine, are secreted. Glucagon stimulates the liver to provide a source of endogenous

glucose through glycogenolysis and gluconeogenesis. Epinephrine has many effects, including the stimulation of hepatic glycogenolysis and gluconeogenesis, mobilization of muscle glycogen, stimulation of lipolysis, mobilization of gluconeogenic precursors, and decreased utilization of glucose by insulin-sensitive tissues (e.g. muscle). Cortisol and growth hormone also have some minor effects to combat chronic hypoglycemia.

When beta cells become neoplastic, normal glucose homeostasis is no longer maintained; insulin is secreted independently of the plasma glucose levels leading to severe hypoglycemia. [14] In the face of hypoglycemia, this inappropriate hyperinsulinemia inhibits glucose release by the liver and increases the utilization of glucose by insulin-sensitive tissues (e.g. muscle, adipose tissue). This leads to chronic hypoglycemia and the resulting clinical signs.

Differential diagnosis

Patients with insulinomas may present with a history of vague clinical signs (e.g. weakness), a normal physical exam, and even normal blood work (normoglycemic). In these cases, diagnosis may be challenging due to the wide range of differential diagnoses. However, sometimes the association of clinical signs with exercise, an extended fast, or feeding may give a clue to the cause. Fasting of the patient may be required before hypoglycemia is apparent. [14] Once the finding of hypoglycemia is made and confirmed, differential diagnoses need to be ruled out. Mechanisms of fasting hypoglycemia include excessive uptake of glucose by normal or neoplastic cells, impaired hepatic gluconeogenesis and glycogenolysis, deficiency in diabetogenic hormones, inadequate dietary intake of glucose and gluconeogenic substrates, or a combination of these mechanisms. [14] Differential diagnoses include insulinoma, extra-pancreatic neoplasia (e.g. hepatocellular carcinoma, hepatoma, leiomyosarcoma), portosystemic shunt, hepatic failure (i.e. cirrhosis or necrosis), sepsis, hypoadrenocorticism, neonatal or

juvenile hypoglycemia, insulin overdose, xylitol toxicity, glycogen storage disorders, and severe pancreatitis, among a few other rare causes. [18] With the patient's signalment, history, normal physical exam, and normal blood work (aside from hypoglycemia), many differential diagnoses such as juvenile hypoglycemia, xylitol toxicity, sepsis, hepatobiliary disease, hypoadrenocorticism, and others may be ruled out, especially with ultrasound and additional bloodwork such as liver function tests and resting cortisol and/or ACTH stimulation tests. Imaging, such as abdominal ultrasound, thoracic and abdominal radiographs, and possibly CT scans, is then used to rule out other differential diagnoses such as extra-pancreatic neoplasia.

Diagnostic Approach/Considerations

In patients with insulinoma, aside from hypoglycemia, a complete blood count, chemistry profile, and urinalysis will usually be normal. [14] In some cases, hypoglycemia may not be present at the time of examination; the patient must be fasted and blood glucose levels checked every 1-2 hours to determine if hypoglycemia occurs. Thoracic and abdominal radiography usually reveal normal findings due to the small size of most insulinomas and the low risk of pulmonary metastasis. [14] Sensitivity of abdominal radiography to detect primary pancreatic neoplasia has been reported as 19%.[10] Abdominal ultrasonography is variable in detecting insulinomas and their metastases, with a sensitivity of identifying the primary pancreatic lesion reported from 22% to 69%. [6, 10, 12, 17] This variability is due to differences in ability to visualize the pancreas (e.g. intestinal content, body conformation), differences in the size of the lesions, and operator and equipment inequality.[8, 17]

Measurement of baseline serum insulin concentration when the blood glucose is less than 50-60 mg/dL is used to confirm the diagnosis of a beta cell tumor. [14] An insulin level within the high end of the reference range or exceeding the reference range is inappropriate when

hypoglycemia is present and is diagnostic for insulinoma.[14] Insulin-to-glucose ratios have previously been utilized to interpret insulin and glucose results; however, these ratios lack specificity and are no longer recommended for use.[18] Measurement of serum fructosamine concentrations may be useful in cases suspected of insulinoma that maintain a fasting glucose above 60 mg/dl.[14] If the fructosamine concentration is below reference range, it supports the existence of a significant period of hypoglycemia.[14] This is supportive of insulinoma but can also be caused by other disorders. Provocative tests such as glucagon, glucose, and tolbutamide tolerance tests and an epinephrine stimulation test are no more useful than the insulin and glucose measurements and can potentially induce fatal hypoglycemia.[14]

Advanced imaging is important for surgical planning to locate the primary pancreatic lesion and for staging. Computed tomography has been reported to detect 71% of primary pancreatic lesions and 40% of metastatic lesions.[17] Additional methods such as single proton emission computed tomography, contrast-enhanced ultrasonography, and somatostatin receptor imaging have been described for the detection of insulinomas.[7, 8, 23]

Treatment and Management

Treatment of insulinomas begins with management of the acute hypoglycemic crisis. At home, this involves the owner rubbing a simple sugar solution on the pet's buccal mucosa. Once sternal, the pet should be encouraged to eat a small meal, and then veterinary advice should be sought. In a hospital setting, acute hypoglycemia is treated with a 0.5g/kg slow IV injection of 50% dextrose diluted at least 1:1 with saline.[14] Care should be taken not to administer a large amount rapidly; the tumor can respond to the rapid increase in blood glucose by releasing more insulin leading to a severe rebound hypoglycemia. The goal of therapy is to control seizures, not correct hypoglycemia. A dextrose constant rate infusion (CRI) can be started following the

bolus. If the dextrose is not effective, a glucagon CRI can be considered. Although there are minimal studies on the use of glucagon CRIs for treatment of hypoglycemia, it has been shown to increase blood glucose to within normal range and allow maintenance of euglycemia.[5] In a retrospective study of 9 patients, all patients experienced increases of blood glucose while on glucagon compared to measurements obtained before glucagon administration. [5] Additionally, five out of 9 patients were successfully weaned from the glucagon CRI with no recurrence of hypoglycemia. [5] The only adverse effect attributed to glucagon CRI recorded was mild hyperglycemia. [5]

Surgical and medical management options are available for the long term management of insulinomas. Surgery is the treatment of choice because it allows for the removal of the primary tumor (via partial pancreatectomy) and detectable metastatic lesions. Although a cure is not usually obtained, surgery can allow patients to go into remission and/or respond better to medical management. [14] The success of the surgery relies on the nature and location of the primary tumor (body vs limb) and extent of metastasis. Most insulinomas can be visualized and/or palpated during surgery; however, rarely they are more difficult to identify. [14] Intravenous infusion of methylene blue has been used for intraoperative identification of the primary tumor; the hyperfunctioning tissue should stain more intensely than the normal tissue. [14] Methylene blue can have serious side effects, including Heinz body hemolytic anemia and acute kidney failure, that must be considered prior to use. [14] The most common complication of a partial pancreatectomy is pancreatitis, which in some cases can be severe and potentially life threatening if aggressive treatment is not initiated. Other side effects include persistent post-operative hypoglycemia or hyperglycemia due to a (usually) transient diabetes mellitus. [14] Surgery may

not be recommended for inoperable tumors located in the body of the pancreas, extensive metastasis, or due to a patient's anesthetic risks.

When surgery is not performed or when clinical signs recur despite surgery, medical management should be initiated. The goal of therapy is to control clinical signs but not necessarily increase glucose to within normal range. One part of medical management involves small frequent feedings of a diet containing high fat, complex carbohydrates, and fiber to allow for a continuous source of glucose and prevention of excessive insulin secretion. [14] Limiting exercise and stress can also help in the control of clinical signs.[14] Glucocorticoids are the next line of therapy after diet change. Glucocorticoids antagonize the effects of insulin at the cellular level, stimulate hepatic glycogenolysis, and indirectly provide the necessary substrates for hepatic gluconeogenesis. [14] Prednisone or prednisolone is used most often starting at a dose of 0.25mg/kg every 12 hours and increasing as needed to control clinical signs. [14] Additional therapy should be considered when diet and glucocorticoids no longer control clinical signs or if the adverse effects of the steroids are no longer tolerated by the owner (usually when the dose reaches 2mg/kg/d). [14] Additional therapies can include diazoxide, octreotide, and streptozotocin. [14] Diazoxide is a benzothiadiazide diuretic that inhibits insulin secretion, stimulates hepatic gluconeogenesis and glycogenolysis, and inhibits tissue use of glucose. [14] However, its use has been limited by its cost and inconsistent availability. Octreotide is a somatostatin analog that inhibits the synthesis and secretion of insulin by normal and neoplastic beta cells. [14] Although octreotide can significantly decrease insulin levels, there are some downsides to its use such as cost, administration by injection only, relatively short effect, and development of a refractory state in some dogs. [14] Streptozotocin is an antineoplastic agent that selectively destroys beta cells. [14] It has a similar structure to glucose and is uptaken by GLUT-2 transporters, which are

of high concentration on beta cells. [14] Within the beta cells, streptozotocin depresses NAD and NADH activity. [14] This drug is extremely nephrotoxic, and a fluid diuresis protocol has been described which decreases the nephrotoxicity. [13] Other side effects include anorexia, vomiting, diarrhea, increased liver enzymes, and diabetes mellitus. [14] In one study, the streptozotocin-treated group's median survival time was not significantly different from the control group's. [13] In another study, the response could not be adequately evaluated due to lack of controls and use of concurrent therapies. [15] Because of the unknown efficacy and serious potential complications, the risks versus benefits must be closely evaluated prior to use. Alloxan is another chemotherapeutic that targets pancreatic beta cells, but it can also have similarly severe side effects such as nephrotoxicity and acute respiratory distress syndrome. [4] Its use has not been extensively studied.

Expected Outcome and Prognosis

Because of the high rate of metastasis, long-term prognosis for insulinomas is guarded to poor. Clinical behavior of insulinomas vary, and disease free intervals and survival times can be hard to predict. Prognostic indicators that have been evaluated include tumor size, TNM (tumor, node, metastasis) stage, fibrosis within the tumor, and Ki67 index. [2] Ki67 is a proliferation marker expressed during the active phases of the cell cycle and absent from resting cells. A higher Ki67 index has a poor prognosis, as does larger tumor size, higher TNM grade, and increased stromal fibrosis within the tumor. [2] Dogs with stage 1 disease (tumor confined to pancreas) have been shown to have a median survival time (MST) of 18 months verses patients in stage 2 or 3 (regional lymph node metastasis and distant metastasis) having a MST of only 6 months. [3]

Patients that undergo both surgery and medical management have longer disease free intervals and survival times. One recent study showed a MST of 1316 days for dogs that underwent surgery then medical therapy (prednisone +/- diazoxide) at the time of relapse. [16] MST for dogs that had a partial pancreatectomy but no medical therapy afterward was 785 days. [16] Dogs that had only medical therapy and no surgery performed were more likely to have a higher stage of disease, and their MST was 196 days. [16] MST of all 28 dogs in this study was 547 days. [16] Another study of outcome for surgical versus medical management showed a MST of 74 days for medical management only, and 381 days for surgical management. [20] Yet another report revealed a MST of 258 days for dogs that underwent a partial pancreatectomy. [21] Of these statistics, the range extends to almost 6 years post-partial pancreatectomy, indicating that some patients can do extremely well following surgery. [16]

Conclusion

Insulinoma is a pancreatic beta cell tumor that inappropriately secretes insulin leading to chronic hypoglycemia. Ruling out other causes of hypoglycemia increases the suspicion of insulinoma. The confirmatory test is an insulin level within the high end of the normal range or exceeding normal range with a concurrent low blood glucose (<50-60 mg/dl). Partial pancreatectomy is treatment of choice, and subsequent medical management with dietary modification and glucocorticoids. Prognosis is generally poor to guarded, due to high rate of metastasis and recurrence of clinical signs.

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