Hypoglycemia in a Boxer

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Introduction

Although rare, insulinoma is the most common endocrine pancreatic neoplasia in dogs and is often malignant. Large breeds are predisposed, with several sources showing an increased rate in boxers, golden retrievers, labs and German shepherds, with no sex-based predispositions noted.[2,4,6] Diagnosis can be difficult as signs are often nonspecific and related to hypoglycemia; common presenting complaints include seizures, weakness, and tremors.[2] Animals are often intermittently symptomatic for a few months before initial presentation. These symptomatic episodes are often related to exercise, fasting, excitement, or feeding.[4]

Case History & Presentation

Duchess was a 7-year-old female spayed Boxer who presented to a nearby emergency clinic on December 23, 2017 for weakness. Prior to this presentation, she had a history of a seizure two weeks before presentation and another the following week. Both episodes occurred after eating hamburgers. Duchess was taken to her primary veterinarian after the first seizure. They discovered hypoglycemia, prescribed a glucose supplement, and recommended trying to get her to eat regular dog food. On presentation at the emergency clinic, a CBC, serum chemistry, and abdominal and thoracic radiographs were performed. There were no significant findings on the radiographs. The CBC showed a mild leukopenia. Serum chemistry showed a mildly increased phosphorus and creatinine, as well as a mild hypokalemia. The most significant finding was severed hypoglycemia at 29 mg/dL. The emergency clinic treated with 5% and 7.5% IV dextrose and a recovery diet to raise serum glucose. Due to lack of progress, she was referred to MSU-CVM on December 26, 2017. Upon presentation, she was bright and alert with no clinical signs noted; thus, dextrose was discontinued. At presentation, her blood glucose was 38 mg/dL. Three hours later, another seizure occurred, and 30 mL of dextrose was administered. Duchess had five more seizures in

the next 6 hours, with two uses of diazepam as a rescue drug. Throughout this time blood glucose fluctuated between 20 to 60 mg/dL.

Pathophysiology

Maintenance of normal blood glucose levels involves a delicate balance of numerous hormones, including glucagon, somatostatin, insulin, and others. Glucagon is secreted by the α cells of pancreatic islets and functions to increase blood glucose levels. Somatostatin is secreted by the γ cells of the pancreas and has numerous functions. With respect to insulinoma, somatostatin depresses both glucagon and insulin production. Insulin is produced by and secreted from the pancreatic β cells. It functions to decrease blood glucose through a variety of methods. Many cells, such as those of muscle, liver, and fat, require insulin to be able to absorb glucose. Insulin also decreases hepatic gluconeogenesis and increases both hepatic and muscle glycogen synthesis.[4]

Pancreatic β cells also do not require insulin to absorb glucose; rather, glucose is transported into β cells at a rate proportional to blood glucose levels. This allows the β cells to respond appropriately to shifting blood glucose levels. Normal β cells respond to increased blood glucose (above 100-110 mg/dL) by secreting insulin. This secretion and synthesis of insulin is then stopped when blood glucose falls below 60 mg/dL.[4]

At low blood glucose levels (<60 mg/dL), counter regulatory hormones work to increase blood glucose and ensure the remainder is spared for tissues dependent on glucose for energy: the central nervous system, bone marrow, renal medulla, and red blood cells.[6] Glucagon and epinephrine increase hepatic gluconeogenesis and glycogenolysis.[4,6] Epinephrine also helps to mobilize glucose precursors (e.g., lactate and glycerol). Cortisol and growth hormone act when blood glucose remains chronically low, promoting lipolysis and protein catabolism to facilitate gluconeogenesis.[6]

In the case of insulinomas, neoplastic β cells are not inhibited by hypoglycemia and continue to synthesize and secrete insulin. These cells do still respond to increases in glucose, such as eating, that would normally stimulate insulin secretion. However, these responses are exaggerated and often result in marked hypoglycemia. The constant high insulin levels increase tissue uptake of glucose, preventing normal glucose sparing mechanisms. Gluconeogenesis and glycogenolysis also are suppressed by these high insulin levels. As the central nervous system is dependent on glucose for energy and has minimal reserves, the CNS is usually the area most affected by hypoglycemia.[6] *Neuroglycopenia*—hypoglycemia within the central nervous system—can cause clinical signs, including lethargy, weakness, abnormal behavior, and seizures.[4] Other signs, such as muscle tremors, shaking, and restlessness, are the result of sympathetic nervous system stimulation.[6]

Differential Diagnoses

Differential diagnoses for hypoglycemia are numerous and include toxicities, hypoadrenocortism, hepatic insufficiency, sepsis, paraneoplastic syndromes, and of course, insulinoma.[2,6] Often there are signs hinting at these in the history, physical exam, or bloodwork. Common toxicities include xylitol ingestion and insulin overdose. Insulin overdose usually occurs in diabetic animals and there should be a history of diabetes. Xylitol is a sugar alcohol used as a sugar substitute in many products. Xylitol ingestion leads to insulin secretion and subsequent hepatic failure in dogs. Careful history taking can help to rule out both, and treatment should be started immediately to address the severe hypoglycemia. Sepsis can also cause hypoglycemia, although the pathogenesis is unclear and likely multifactorial. Animals with sepsis-induced hypoglycemia should show signs of infection on both physical examination and CBC. These animals are usually debilitated. CBC often shows severe leukocytosis with toxic changes and a left shift.

Along with toxicities and sepsis, chronic conditions should be considered during diagnostic examinations. Hypoadrenocorticism, also called Addison's disease, results in hypoglycemia because of glucocorticoid deficiency. Characteristic electrolyte abnormalities, such as hyperkalemia and hyponatremia, should be seen on a serum chemistry. In addition, animals with Addison's disease may have mild lymphocytosis and eosinophilia. However, atypical hypoadrenocorticism may cause hypoglycemia without electrolyte disturbances. If suspicious, a baseline cortisol or ACTH stimulation test can be used to rule out hypoadrenocorticism. Hepatic insufficiency can occur as a congenital abnormality, such as with portosystemic shunts, or be acquired from severe liver damage. Congenital abnormalities usually present in much younger animals. In cases of acquired liver damage, liver enzymes, including ALT and AST, are elevated due to hepatocyte damage. In both cases, BUN, blood glucose, and albumin are usually decreased as the liver is unable to produce them. A liver function test can be used to rule out hepatic insufficiencies. Paraneoplastic hypoglycemia can occur with many neoplasms but is most commonly associated with hepatocellular carcinoma, hepatoma, and leiomyosarcoma. The cause of paraneoplastic hypoglycemia is complicated and can be due to excessive glucose use by the tumor, impaired hepatic glycogenolysis and gluconeogenesis, or secretion of IGF-1. If these tumors are large, they may be felt upon palpation of the abdomen. In addition, those associated with the liver often cause increased liver enzymes. These tumors may also be visualized on radiographs or ultrasound.[6] Finally, insulinomas can be confirmed with paired glucose and insulin levels. In cases of paraneoplastic hypoglycemia, both blood glucose and insulin will be low. In cases of insulinomas, blood glucose will be low and insulin levels will be inappropriately high.[2]

Diagnostic Approach/Considerations

Physical exam findings are often insignificant with no obvious abnormalities. Some dogs may show weakness, lethargy, mild weight gain, or tremors.[4,6] The severity of these signs is dependent on the duration and severity of hypoglycemia. Often animals can compensate more for chronic hypoglycemia than for acute changes to blood glucose. However, in those animals, small additional changes to blood glucose, such as with exercise or feeding, result in symptomatic episodes.[6] Other physical exam findings can include muscle atrophy, paresis or paralysis, and decreased reflexes. These findings are due to peripheral neuropathies of uncertain pathogenesis. These peripheral neuropathies may not respond to treatment and correction of hypoglycemia; thus, prognosis for resolution is guarded to poor.[6]

The main clinic-pathologic abnormality associated with insulinomas is decreased blood glucose. A second blood sample should be used to confirm this hypoglycemia, particularly if there was any delay in testing the original sample. This hypoglycemia can be significant with one study reporting a mean of 42 mg/dL.[6] However, this can also vary, and some dogs may have a blood glucose above 60 mg/dL.[6] In these animals, fasting with hourly monitoring of blood glucose should be used to evaluate for hypoglycemia. Hypoglycemia should occur within 12 hours in dogs with insulinomas. CBC and urinalysis are often unremarkable. Serum chemistry may reveal increased liver enzyme activity; however, there has been no definitive link between liver enzyme activity and metastasis to the liver.[6] Paired glucose and insulin levels are used to confirm the presence of an insulinoma.[2,4]

Imaging information is useful to staging of insulinomas and surgical planning. In terms of staging, animals with distant metastases have a poorer prognosis than those with insulinomas restricted to the pancreas and regional lymph nodes. As 40% to 50% of insulinomas have already metastasized at the time of diagnosis, identification of these metastases is crucial for determining prognosis and surgical planning. Additionally, imaging

ideally would assist localize of insulinomas within the pancreas. Localization can affect surgical planning of the approach to access the appropriate section of the pancreas.[3]

Radiographs frequently are not useful in diagnosis of insulinoma, mainly due to the small size of insulinomas. These tumors are usually smaller than 3 cm at the time of diagnosis. Further, common sites of metastases are the liver, regional lymph nodes, and nearby omentum, which are not easily evaluated with radiographs.[6]

Ultrasound and CT can be used to identify pancreatic masses, rule out other neoplasms, and identify potential metastases. Localization of pancreatic masses is important to assess whether the tumor can be resected. Potential metastases can impact future treatment, complications, and prognosis.

Ultrasound can help to show a mass in the region of the pancreas, as well as metastases in the liver and local lymph nodes. However, most insulinomas are small and of similar echogenicity as the surrounding tissue. As such, ultrasound findings may be normal. Ultrasound also may identify metastases of the liver without visualizing the primary pancreatic mass. Ultrasound has been shown to have a sensitivity ranging from 35% to 69% in identifying insulinomas.[6] Normal ultrasound findings do not exclude the possibility of an insulinoma.[6]

Contrast enhanced CT has been shown to be very sensitive (96%) in detecting the presence of an insulinoma; however, localization using contrast-enhanced CT was significantly less sensitive (52%) in one retrospective study.[3] Contrast-enhanced CT was also less than ideal in identifying metastases, with a sensitivity of 67% in identifying lymph node metastases and a sensitivity of 75% in identifying liver metastases. This unsatisfactory localization and metastases identification are a result of the heterogenous enhancement patterns of insulinomas and lack of a specific post-contrast phase in which insulinomas are easily visualized. MRI has been shown to be more sensitive in detecting the presence and

location of human insulinomas.[3] However, canine abdominal studies are lacking and inconsistent. Further research for use of MRI in canine abdominal studies may show that it is more accurate in identifying insulinoma locations over contrast enhanced CT. With current imaging techniques and knowledge, correct localization of canine insulinomas and their metastases is difficult and impacts surgical planning.[3]

Treatment & Management

Treatment of insulinomas varies based on the site of the insulinoma, presence of metastases, and concurrent illnesses.[6] The treatment of choice is surgical resection of the tumor and any metastases.[2] Even in cases where the tumor or metastases are not fully resectable, debulking can ameliorate or completely alleviate clinical signs.[6] Medical management is necessary prior to surgery to make the animal a better anaesthetic candidate.[4] Pre-operatively, frequent small meals and glucocorticoids should be used to prevent severe hypoglycemic episodes. Fluid therapy with a balanced electrolyte solution with 2.5-5% dextrose should be used perioperatively to reduce complications. This helps to maintain pancreatic blood flow which can minimize the risk of post-operative pancreatitis. The dextrose helps to prevent clinical signs related to hypoglycemia.[6] Dogs with insulinoma benefit from the addition of medetomidine to the pre-anaesthetic medications. This medicine has been shown to decrease insulin levels and increase glucose concentrations in dogs with insulinoma undergoing surgical removal.[5] Further, less glucose supplementation was needed in dogs with insulinoma that received medetomidine as compared to those that did not. Animals that received medetomidine also had significantly less blood pressure fluctuations and needed less additional analgesic or anaesthetic drugs than those that did not.[5]

During surgery, glucose should be monitored every 30 to 60 minutes. Gentle handling of the pancreas is vital to decrease the chance of post-operative pancreatitis. The pancreas, liver, local lymph nodes, and the surrounding omentum should be assessed as thoroughly as

possible for metastases. The location of the tumor significantly impacts the success of surgery. Tumors in the right or left limb of the pancreas are more amenable to complete resection with less handling and subsequent pancreatitis. Tumors in the pancreatic body may not be able to be completely resected and are more complicated to remove due to the presence of the pancreatic ducts, blood vessels, and lymphatics. For these tumors, more handling of the pancreas results in higher rates of more severe post-operative pancreatitis.[2,6] There is also a higher rate of hypoglycemia recurrence after surgery due to remaining functional neoplastic cells. Common post-operative complications include pancreatitis of varying severity, recurrence of hypoglycemia, and transient hyperglycemia.[6]

After surgery, glucose levels should continue to be monitored. Small, frequent meals of a low-fat diet acceptable for pancreatitis should be given as soon as possible after surgery. Pre-emptive treatment for pancreatitis, even without enzyme level confirmation, can also help to decrease complications. Based on the glucose levels, either insulin therapy or additional medical management for hypoglycemia should be instituted. Long-term, fasting blood glucose should continue to be monitored for recurrence. If fasting blood glucose falls below 70 mg/dL, insulin levels should be assessed for recurrence.[6]

If clinical signs recur, medical management can be used. Medical management also is used for cases where surgery is not an option or if surgical removal is incomplete. Medical management is aimed at alleviating the clinical signs rather than preventing metastasis or tumor growth.[6] Medical management starts with small, frequent meals that are low in simple sugars to help prevent insulin spikes following increases in blood glucose.[2] Exercise and excitement should be limited as much as possible. These can lead to acute hypoglycemia by increasing muscle use and uptake of glucose.[4] Administration of glucocorticoids is used to cause insulin resistance and increase hepatic gluconeogenesis.[2] Streptozotocin, an alkylating agent, is very similar in structure to the glucose transporter 2 present on both neoplastic and

normal pancreatic β cells and is selectively toxic to pancreatic β cells. Fluid diuresis should be done with streptozotocin administration to decrease the risk of kidney damage.[7] In addition to kidney damage, this drug may lead to gastrointestinal signs, pancreatitis, and the development of diabetes mellitus that can limit its use.[6,7] Octreotide is a somatostatin analogue shown to decrease plasma insulin levels and increase blood glucose levels in dogs with insulinoma, although this effect is somewhat delayed. It may also influence gastrointestinal glucose absorption and metabolism of glucose.[8] Diazoxide is a diuretic that can cause hyperglycemia by inhibiting insulin secretion and tissue use of glucose. It also stimulates hepatic gluconeogenesis and glycogenolysis.[6] These treatments can be used in combination at the discretion of the attending clinician. Adverse effects are common with medical therapy, with the most common being gastrointestinal signs, such as vomiting and anorexia. Development of diabetes mellitus can occur either transiently or long-term. This should be discussed with the clients thoroughly prior to treatment.[2,6,7]

Prognosis

Long-term prognosis for dogs with insulinoma is poor; this is partially because nearly all canine insulinomas are malignant.[2,4,6] However, the median survival time and remission of clinical signs can widely vary. TMN (tumor-node-metastasis) stage of disease and type of treatment can affect the prognosis.[6] Surgical resection offers longer remission of clinical signs and improved survival over medical management alone.[2,4,6] With surgical treatment, survival time is between 12 to 14 months in several studies.[4] Dogs with stage 1 insulinoma—restricted to the pancreas—were normoglycemic for 14 months post-surgery.[2,4,6] Less than 20% of those dogs with stage II—pancreas and regional lymph nodes involved—and stage III—metastasis to distant organs—were still disease free at 14 months post-surgery.[4] At 6 months post-surgery, less than 50% of dogs with stage III were still alive[2,6] and all were deceased by 18 months.[4,6]

Other prognostic indicators include tumor size, stromal fibrosis, and the Ki67 index. As would be expected, larger tumors resulted in a poorer prognosis and shorter survival time. Stromal fibrosis is noted to be a significant prognostic indicator in these tumors and points to more aggressive tumors with decreased survival times.[1] A proliferation marker, Ki67, also has been found to be a predictive prognostic indicator.[1,6] Those tumors with a high expression of Ki67 have a poorer clinical outcome.[1]

Case Outcome

Hypertonic saline was initiated to treat suspected increased intracranial pressure due to damage occurring from the seizures. Glucagon was used to attempt to increase and maintain higher blood glucose levels. Duchess continued to have seizures about every 30 minutes. After the 6th seizure, a Cushing's reflex was seen, and mannitol was initiated. Duchess continued to decline and was euthanized. Necropsy revealed three 1-3 cm masses on the right limb of the pancreas. These masses were subdivided by fibrosis and stained positive for insulin. No metastases were noted.

Conclusion

Insulinomas are functional neuroendocrine tumors of the pancreatic β cells. These tumors secrete high levels of insulin and are resistant to normal feedback mechanisms, causing profound hypoglycemia and subsequent central nervous system dysfunction. The treatment of these tumors is aimed at remission of clinical signs, rather than a cure. Surgical resection of the tumor is ideal and results in longer disease-free intervals and survival rates. Medical management can also be used when surgery is not an option or as an adjunct to surgical resection. The long-term prognosis for these tumors is poor; however, survival times are highly variable.

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