Insulinoma in the Canine

Clinicopathologic Conference

Timothy J. Sullivan
Mississippi State University College of Veterinary Medicine
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Advisor:
Todd Archer, DVM, MS Diplomate ACVIM

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Introduction

The pancreas is a glandular organ in the cranial abdomen that has both endocrine and exocrine functions. The exocrine pancreas is responsible for the production of pancreatic enzymes, which are carried to the descending duodenum by pancreatic ducts, and which aid in the digestion of carbohydrates, fats, and proteins. The islet cells of the pancreas secrete insulin and glucagon into the blood, which keep the systemic blood glucose concentrations within a tight range needed for normal daily functions. Insulinomas are functional tumors of the B cells of the pancreas that secrete excessive amounts of insulin in the face of hypoglycemia, which would normally halt the production and secretion of insulin due to the normal feedback control. In addition, immunohistochemical analysis of beta-cell tumors has revealed a high incidence of multi-hormonal production, including pancreatic polypeptide, somatostatin, glucagon, serotonin, and gastrin[1,2,3].

The clinical signs associated with insulinomas are caused by insulin induced hypoglycemia, as unregulated production of insulin leads to low blood glucose. With an acute drop in blood glucose, CNS signs develop before other signs are noticed, including seizures, weakness, and dull mentation.

Insulinomas are uncommon in the dog and ferret and rare in the cat.[4] Increased incidence has been suggested in large breed dogs with no sex predication.[4] An insulinoma should be highly suspected in animals that are hypoglycemic while maintaining a high blood insulin level. The prognosis is guarded to poor with a median survival time after diagnosis of only 74 days in dogs treated medically, compared to 381 days in dogs that initially underwent surgery.[5]

History and Presentation

The case presented is an approximately 5-year-old spayed female Siberian Husky, Willow. Willow was a stray dog which who was adopted by her owner in 2014. On 5/24/16, the owner noticed Willow was sluggish and stumbled during one of her walks. Up to this point, Willow was apparently healthy. A few days after the stumbling episode, Willow let out a scream/yelp and demonstrated signs that the owner worried was a seizure. This same seizure like activity happened twice more that night and she was taken to a veterinary hospital in Memphis on emergency.

At presentation on 5/31/16 in Memphis, blood work revealed a glucose of 32 mg/dl. She was placed on a 5% dextrose IV drip at 4ml/kg/hr and monitored overnight, of which her highest recorded glucose was 97 mg/dl. Willow was discharged the next morning, but unfortunately she suffered another seizure shortly after returning home. She was taken back to the emergency hospital where a blood sample was collected for a paired glucose/insulin measurement. This blood test was sent out to ANTECH for analysis. Addison's disease was ruled out as a cause of hypoglycemia using an ACTH stimulation test, with results of a baseline cortisol of <1.0 mcg/dL and a post ACTH stim cortisol of 3.8 mcg/dL. She was prescribed Keppra (levetiracetam) at 2.5 mg/kg for seizures and started on prednisone at 0.5 mg/kg q 24h. On 6/6/16, Willow was euglycemic all day and was referred to MSU-CVM Internal Medicine Service for a further work-up and treatment.

Willow presented to MSU-CVM Internal Medicine Service on 6/7/16. Upon presentation Willow was quiet, alert, and responsive. Her vital parameters were within normal limits. She had a rectal temperature of 101.5F, a pulse of 112 beats per minute, and respiratory rate 88 breathes per minute. Her heart and lungs auscultated normally and there were no abnormalities on

abdominal palpation. Willow was slightly overweight with a BCS of 6/9. The rest of her physical exam was unremarkable. Initial diagnostics included a complete blood count, serum chemistry, and urinalysis, which revealed a stress leukogram, mild azotemia, and mildly elevated liver enzymes. While awaiting the paired glucose/insulin test results which were sent out, thoracic and abdominal radiographs were performed which revealed no significant findings. A CT scan was also performed which revealed a large pancreatic mass in an area of the right limb of the pancreas measuring 2.2 cm x 2.1 cm x 3 cm. Willow was placed in ICU overnight with IV dextrose for rescue while waiting for the results from the insulin/glucose test to be finalized.

On 6/8/16 the results from the paired glucose/insulin test sent to ANTECH by the referring veterinarian returned and revealed an insulin concentration of 46.4 mcU/mL (HIGH) and a blood glucose concentration of 68mg/mL (LOW). A fasting sample was also sent and revealed a blood glucose concentration of 28mg/mL (LOW) and an insulin concentration of 35.2 (HIGH) mcU/mL. At this point Willow, had clinical signs consistent with an insulinoma, hypoglycemia with concurrent hyperinsulinemia, and a pancreatic mass found on CT. These three clinical features made the diagnosis of insulinoma highly probable.

Pathophysiology

The panaceas is made up of two major types of tissue: the acini and the islet of Langerhans. The islets contain three major types of cells, alpha, beta, and delta cells, which are distinguished from one another by their morphological and staining characteristics.[6] The beta cells, consisting of about 60% of all the cells of the islets, lie mainly in the middle of each islet and secrete insulin. [7,8] Insulin regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of glucose from the blood into fat, liver and skeletal muscle cells.

To maintain homeostasis, the body has mechanisms in place to keep glucose concentrations within the physiologic range. Insulin secretion rates respond to changes in blood glucose concentration. An increase in blood glucose levels results in an increase in the rate of glycolysis and a corresponding increase in the rate of insulin secretion by the beta cell, and vice versa.[6,]

When the blood glucose concentration decreases toward the lower limit of the normal physiologic range, insulin synthesis and secretion is inhibited, which limits tissue utilization of glucose and allows the blood glucose concentration to increase.[9] If the blood glucose concentration decreases below the normal reference range, increased secretion of glucose counter-regulatory hormones, most notably glucagon and epinephrine in the immediate phase of hypoglycemia and cortisol and growth hormone in the chronic phase of hypoglycemia, all working to increase the blood glucose concentration back into the normal physiologic range. [6]

The endocrine system plays a huge role in the regulation of glucose within the body. In a healthy patient, when blood glucose concentrations decrease below 60 mg/dl, insulin secretion stops, and catecholamines and glucagon are released to help return the blood glucose concentration to normal.[10] In animals with insulinoma, neoplastic beta cells continue to secrete insulin despite hypoglycemia and counter-regulatory control.

Glucose is the main source of energy of the brain and is therefore critical to its function. Clinical signs associated with insulinoma are directly related to the insulin-induced hypoglycemia. Signs include posterior weakness, fatigue after exercise, generalized muscular twitching and weakness, ataxia, mental confusion, and changes of temperament. The onset of clinical signs is related to both the degree of hypoglycemia achieved and the rate at which it occurs.[6]

In dogs, insulinoma develops in the right and left pancreatic lobes with equal frequency. Solitary nodules are most common, but multiple nodules and occult nodules can occur. Virtually all beta-cell tumors in dogs are malignant (95%) and up to 64% have metastatic lesions at the time of surgery. Metastasis to the liver, regional lymph nodes, and omentum is most common[10,5]

Diagnostic Approach/Considerations

Insulinomas occur in middle aged to older dogs with an average age of nine years.[11] There is no sex predication. Large breeds are most commonly diagnosed but no studies have been able to show breed specificity. In the dog, common clinical signs include seizures, weakness, collapse, muscle twitching or other bizarre behavior. The severity of these signs depend on the severity of hypoglycemia. On physical exam there are usually no significant abnormalities. Due to the anabolic effects of insulin, dogs commonly are overweight.[12] Complete blood counts show no significant abnormalities. The main serum chemistry abnormality is hypoglycemia however a normal blood glucose concentration does not rule out insulinoma.[10] Serum chemistry may also show mild hypokalemia and elevated liver enzymes.[13] Urinalysis is also unremarkable.

When suspecting insulinoma, simultaneous measurement of serum glucose and insulin concentrations should be made when the blood glucose concentration is <60 mg/dl (<3.2 mmol/L). [10] At this concentration, insulin is normally suppressed. Hyperinsulinemia during hypoglycemia is strongly supportive of the diagnosis of insulinoma. If an insulinoma is suspected but the blood glucose concentration is normal, the patient should be fasted and blood glucose concentrations assessed every 1-2 hours, with collection of a sample for concurrent

insulin measurement when hypoglycemia is present.[10] A low serum fructosamine concentration may also be used and will show chronic hypoglycemia over the previous 1-2 weeks.

Thoracic and abdominal radiographs are usually normal in patients with insulinoma but can be used to rule in/out other differentials. Insulinomas rarely metastasize to the lungs and it is usually later in the disease process.[5] Ultrasound may be helpful however it should be used in addition to other diagnostic tests. Additional imaging to help identify a nodule in the pancreas can include advanced imaging (CT or MRI).[14] Confirmatory testing involves histologic evaluation and immunohistological staging of the tumor.[14]

In summary, compatible clinical signs, hypoglycemia with concurrent hyperinsulinemia, and the presence of a pancreatic mass support the diagnosis of insulinoma. Histopathologic analysis of the mass is confirmatory. Causes of hypoglycemia in dogs can be found in Table 1:

Causes of Hypoglycemia in Dogs and Cats

Beta-cell tumor (insulinoma)*	Hypoadrenocorticism*	diseases (GSDs)
Extra pancreatic neoplasia	Primary and secondary	Severe malnutrition
Hepatocellular carcinoma, hepatoma*	Idiopathic hypoglycemia*	Prolonged storage of whole blood*
Leiomyosarcoma, leiomyoma*	Neonatal hypoglycemia	Iatrogenic
Hepatobiliary disease*	Juvenile hypoglycemia (especially toy breeds)	Insulin overdose*
Portosystemic shunts	Hunting dog hypoglycemia	Sulfonylurea therapy
Chronic fibrosis, cirrhosis	Exocrine pancreatic neoplasia	Ethylene glycol ingestion
Hepatic necrosis; toxins, infectious agents	Pancreatitis	Xylitol ingestion
Primary and metastatic neoplasia	Glucagon deficiency	Alpha lipoic acid
Sepsis*	Chronic kidney disease	Dried chicken jerky treats
Severe canine babesiosis	Hypopituitarism	Artifact*
Septic peritonitis	Severe polycythemia	Portable blood glucose monitoring (PBGM) devices
	Hepatic enzyme deficiencies	Laboratory error
	Glycogen storage	

Treatment and Management

Initial stabilization is key, especially in emergency situations. The goal of initial stabilization should not be aimed at making the patient euglycemic, rather it should be aimed at increasing glucose concentrations to alleviate clinic signs.[5] Excessive treatment may stimulate further insulin release. If seizures are present, an IV dextrose bolus can be given. Then a CRI of fluids with 2.5% -5% dextrose can be administered at a rate of 1-2mL/kg/h. Glucagon can be given as a CRI in refractory hypoglycemic patients in an acute crisis. If seizures persist, diazepam at 0.5-1 mg/kg IV can be considered until medical management raises the blood glucose high enough to resolve the seizure activity. Medical treatment can be a long-term option but surgery to debulk or remove the tumor often allows for the longest time interval without clinical signs.

In the dog, surgery is the treatment of choice. Before surgery is performed, the patient should give IV dextrose fluids to resolve clinical signs of hypoglycemia. [5] During surgery, a complete inspection of the pancreas should performed. If the pancreas is not handled with care during surgery, pancreatitis may develop. A thorough examination of the rest of the abdomen should be performed to search for any evidence of metastasis.

Since the rate of metastasis is so high in patients diagnosed with insulinoma, long term therapy should be initiated. Diet is the first step in the management of hypoglycemia secondary to insulinoma. Patients should be fed 4-6 small meals per day of a diet high in protein, fat, and complex carbohydrates. Simple sugars should be avoided as they cause the quick release of insulin. Animals should also be restricted in their exercise.

If signs are not under control through diet alone, predisone can be added at a starting dose of 0.25 mg/kg PO q 12h and titrated upwards to a maximum dosage of 1 mg/kg PO q 12h.

Glucocorticoids antagonize the effects of insulin at the cellular level, stimulate hepatic glycogenolysis, and indirectly provide the necessary substrates for hepatic gluconeogenesis.[15]

Additional therapy includes the use of diazoxide, octreotide, and streptozotocin. Diazoxide (Proglycem) is a benzothiadiazide diuretic that inhibits insulin secretion, stimulates hepatic gluconeogenesis and glycogenolysis, and inhibits tissue use of glucose. [6] This leads to an increase in blood glucose. It is important to note diazoxide does not inhibit insulin synthesis. Dosing begins at 5 mg/kg PO q 12h. The dosage may gradually be increased as needed to control signs of hypoglycemia but should not exceed 60 mg/kg/day. In one report, nine of 14 dogs had a good response to diazoxide therapy. [13]

If the patient continues to be unresponsive to therapy, a somatostain analog such as octreotide can be considered. Administration of octreotide can rapidly decrease the serum insulin concentration, causing a corresponding increase in the serum glucose concentration in dogs with insulin-secreting neoplasia.[16] The starting dose is 10-50 mcg/DOG SQ q 8-12h. Questionable efficacy has been reported using this drug. The responsiveness of insulin-secreting tumors to the suppressive effects of octreotide varies and depends on the presence of membrane receptors on the tumor cells that bind somatostatin.[17,18]

Streptozotocin, a naturally occurring nitrosourea that is similar in structure to glucose, is a third option but is highly nephrotoxic. Streptozotocin works by selectively killing beta cells. If used, a 3-hour pre-treatment diuresis and 2-hour post-treatment diuresis are necessary with drug administration which occurs as an IV infusion.[5,10,19] This may be repeated every three weeks.

Case Outcome

Because Willow's diagnosis was so probable for an insulinoma, a surgery consult was arranged and she was transferred for surgery on 6/9/16. On 6/9/2016, a partial pancreatectomy

to remove the tumor was performed along with an abdominal exploration. A marginal duodenum enterotomy was also performed because 2 masses were observed in the duodenum. Surgery was uneventful and Willow recovered from anesthesia with no complications.

Shortly after surgery, Willow's blood glucose began to rise. She was euglycemic within one hour after the tumor was removed. Her blood glucose continued to rise but she did not remain hyperglycemic for more than 24 hours, and so medical intervention was not initiated. She was discharged on 6-11-16 with instructions to see her regular veterinarian 10-14 days post-operatively for a recheck.

Histopathology of the mass confirmed the diagnosis of insulinoma with evidence of intravascular invasion. The section of duodenum submitted revealed a piece of ectopic non-neoplastic pancreatic tissue. After leaving the Animal Health Center at Mississippi State University College of Veterinary Medicine, all rechecks were performed by the referring veterinarian. As of 11/22/16 Willow is reported as doing well.

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