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HYPOGLYCEMIA AND BETA CELL TUMORS
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Functional tumors arising from the beta cells of the pancreatic islets are malignant tumors that secrete insulin independent of the typically suppressive effects of hypoglycemia. Beta cell tumors are uncommon in dogs and rare in cats. The malignant potential of beta cell tumors is often underestimated. In my experience, virtually all such tumors in dogs are malignant and most animals have microscopic or grossly visible metastatic lesions at the time of surgery. The most common metastatic sites are the abdominal lymph nodes, liver, and peripancreatic mesentery and omentum. Pulmonary metastasis is rare. Hypoglycemia typically recurs weeks to months after surgical excision of the tumor. The high prevalence of metastatic lesions at the time dogs are initially examined results, in part from the typically protracted time it takes for clinical signs to develop and the interval between the time an owner initially observes signs and seeks assistance from a veterinarian.

Insulin-secreting tumors typically occur in middle-aged or older dogs and cats and in a wide variety of dog breeds but most commonly large breeds such as German Shepherd Dogs, Labrador Retrievers, and Golden Retrievers. Clinical signs are caused by neuroglycopenia (hypoglycemia) and an increase in circulating catecholamine concentrations and include seizures, weakness, collapse, ataxia, muscle fasciculations, and bizarre behavior. The severity of clinical signs depends on the duration and severity of the hypoglycemia. Dogs with chronic fasting hypoglycemia or with recurring episodes appear to tolerate low blood glucose concentrations (i.e., 1 to 2 mmol/l) for prolonged periods without clinical signs, and only small additional changes in the blood glucose concentration are then required to produce symptomatic episodes. Fasting, excitement, and exercise may trigger the development of clinical signs. Clinical signs tend to be episodic and are generally observed for only a few seconds to minutes because of the compensatory counterregulatory mechanisms that increase the blood glucose concentration when hypoglycemia develops.

The physical examination is unremarkable in the majority of dogs with an insulin-secreting tumor. Abnormalities identified on physical examination include weakness, lethargy, collapsing episodes, and weight gain. Weight gain is probably a result of the potent anabolic effects of insulin. Peripheral neuropathies have been observed and may cause weakness of the rear limbs, proprioception deficits, depressed reflexes, and muscle atrophy. The pathogenesis of the neuropathy is not known. Proposed theories include metabolic derangements of the nerves induced by hyperinsulinemia or an immune-mediated reaction resulting from the sharing of antigens between the tumor and nerves.

The only consistent abnormality identified in routine blood and urine tests is hypoglycemia, which is typically 1.5 to 3.0 mmol/l. Dogs with insulin-secreting tumors may occasionally have a blood glucose concentration of 3.5 to 4.0 mmol/l revealed during random testing. Such a finding does not rule out
hypoglycemia as a cause of episodic weakness or seizure activity. Fasting with hourly evaluations of the blood glucose concentration is usually successful in demonstrating hypoglycemia in dogs and cats with insulin-secreting tumors. The remainder of routine blood and urine test results are usually normal.

The diagnosis of an insulin-secreting tumor requires an initial confirmation of hypoglycemia, followed by documentation of inappropriate insulin secretion and identification of a pancreatic mass using ultrasonography or exploratory surgery. Considering the potential differential diagnoses for hypoglycemia (Table 1), a tentative diagnosis of insulin-secreting neoplasia can often be made on the basis of the history, physical examination findings, and an absence of abnormalities other than hypoglycemia shown by routine blood tests. Abdominal ultrasonography can be used to identify a mass in the region of the pancreas and to look for evidence of potential metastatic disease in the liver and surrounding structures. Most insulin-secreting tumors are small and may not be identified with abdominal ultrasound. Failure to identify a mass with abdominal ultrasound does not rule out an insulin-secreting tumor.

The diagnosis of an insulin-secreting tumor is established by evaluating the blood insulin concentration at a time when hypoglycemia is present. Hypoglycemia suppresses insulin secretion in normal animals. Hypoglycemia fails to have this same suppressive effect on insulin secretion if the insulin is synthesized and secreted from autonomous neoplastic cells. Invariably the dog or cat with an insulin-secreting tumor will have inappropriate excesses in its insulin concentration relative to that needed for a particular blood glucose concentration. The relative excess of insulin is easiest to recognize when the blood glucose concentration is low, preferably less than 2.8 mmol/l. Most dogs and cats with insulin-secreting neoplasia are persistently hypoglycemic. If the blood glucose concentration is less than 3.3 mmol/l (preferably less than 2.8 mmol/l), serum should be submitted to a commercial veterinary endocrine laboratory for determination of the glucose and insulin concentration. If the dog is euglycemic, a fast may be necessary to induce hypoglycemia.

Serum insulin and glucose concentrations must be evaluated from the same blood sample. Serum insulin and glucose concentrations in healthy fasted dogs are usually between 35 and 145 pmol/l and 4.0 and 6.0 mmol/l, respectively. A serum insulin concentration that exceeds 145 pmol/l in a dog with a corresponding blood glucose concentration of less than 3.3 mmol/l (preferably less than 2.8 mmol/l) in combination with appropriate clinical signs and clinicopathologic findings strongly supports the diagnosis of an insulin-secreting tumor. An insulin-secreting tumor is also possible if the serum insulin concentration is in the high-normal range (i.e., 70 to 145 pmol/l). Insulin values in the low-normal range (i.e., 35 to 70 pmol/l) may be found in dogs with other causes of hypoglycemia as well as in those with insulin-secreting tumors. Careful assessment of the history, physical examination findings, and clinical pathologic and abdominal ultrasonographic findings, and possibly repeated serum glucose and insulin measurements, can usually identify the cause of the hypoglycemia. Any serum insulin concentration that is below the normal range (typically less than 35 pmol/l) is consistent with insulinopenia.
and does not indicate the presence of an insulin-secreting tumor. Similar guidelines are used in cats with suspected insulin-secreting tumor. Confidence in identifying inappropriate hyperinsulinemia is dependent on the severity of the hypoglycemia; the lower the blood glucose concentration, the more confident the clinician can be in identifying inappropriate hyperinsulinemia, especially when the serum insulin concentration falls in the normal range.

Treatment for an insulin-secreting tumor involves surgical exploration, medical treatment, or both. Surgery offers a chance to cure dogs with a resectable solitary mass. In dogs with nonresectable tumors or with obvious metastatic lesions, the removal or “debulking” of as much abnormal tissue as possible has frequently resulted in the remission, or at least alleviation, of clinical signs and an improved response to medical therapy lasting for weeks to months. Survival time is also longer in dogs undergoing surgical exploration and tumor debulking followed by medical therapy, compared with dogs only treating medically. Despite these benefits, surgery remains a relatively aggressive mode of diagnosis and treatment, in part because of the high prevalence of metastatic disease, the older age of many dogs and cats at the time beta cell neoplasia is diagnosed, and the potential for post-operative pancreatitis. As a general rule, I am less aggressive about recommending surgery in aged dogs and cats (i.e., 12 years and older), dogs and cats with metastatic disease identified by ultrasonography, and dogs and cats with significant concurrent disease.

Until surgery is performed, the dog or cat with an insulin-secreting tumor must be protected from episodes of severe hypoglycemia. This can usually be accomplished through the frequent feeding of small meals and administration of glucocorticoids (Table 2). During the perioperative period a continuous IV infusion of a balanced electrolyte solution containing 2.5% to 5% dextrose can be used to minimize clinical signs and severe hypoglycemia (<2 mmol/l). If dextrose-containing fluids are ineffective in preventing severe hypoglycemia, a constant rate infusion of glucagon should be considered. Glucagon is a potent stimulant of hepatic gluconeogenesis and is effective in maintaining normal blood glucose concentrations in dogs with beta-cell neoplasia when administered by constant rate infusion. One mg of lyophilized glucagon USP is reconstituted with the diluent provided by the manufacturer and the solution is added to one liter of 0.9% saline, making a 1 µg/ml solution which can be administered by syringe pump. The initial dosage is 5 to 10 ng/kg of body weight/min. The dosage is adjusted, as needed, to maintain the blood glucose concentration within the normal range. When discontinuing glucagon, the dose should be gradually decreased over 1 to 2 days.

Medical treatment for chronic hypoglycemia should be initiated if an exploratory celiotomy is not performed or if the development of metastatic or inoperable neoplasia results in the recurrence of clinical signs (Table 2). The goals of long-term medical therapy are to reduce the frequency and severity of clinical signs and to prevent an acute hypoglycemic crisis, not to establish euglycemia, per se. Medical therapy currently consists of nonspecific antihormonal therapy. This therapy is palliative and should minimize
hypoglycemia by increasing the absorption of glucose from the intestinal tract (frequent feedings); increasing hepatic gluconeogenesis and glycogenolysis (glucocorticoids); or inhibiting the synthesis, secretion, or peripheral cellular actions of insulin (diazoxide, somatostatin).

References


Table 1. Causes of Hypoglycemia in Dogs and Cats (*Common Cause)

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<th>Renal failure</th>
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<td>Carcinoma (mammary, salivary, pulmonary)</td>
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Table 2. Long-Term Medical Therapy for Dogs and Cats with Beta Cell Tumor

Dietary Therapy
- Feed canned or dry food in three to six small meals daily
- Avoid foods containing monosaccharides, disaccharides or propylene glycol

Limit Exercise

Glucocorticoid Therapy
- Prednisone, 0.5 mg/kg divided bid initially
  - Gradually increase dose and frequency of administration, as needed
  - Goal is to control clinical signs, not to reestablish euglycemia
  - Consider alternative treatments if signs of iatrogenic hypercortisolism become severe or glucocorticoids become ineffective

Diazoxide therapy
- Continue standard treatment; reduce glucocorticoid dose to minimize adverse signs
- Diazoxide, 5 mg/kg bid initially
  - Gradually increase dose as needed, not to exceed 60 mg/kg/day
  - Goal is to control clinical signs, not to reestablish euglycemia

Somatostatin Therapy
- Continue standard treatment; reduce glucocorticoid dose to minimize adverse signs
- Octreotide, 10 to 40 µg/dog SC bid to tid