Insulinoma

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Insulinomas are functional tumors of the β cells of the pancreas that secrete excessive amounts of insulin. While insulinomas can produce a variety of polypeptide hormones, hyperinsulinism typically predominates. The clinical signs of hyperinsulinism are due either to neuroglycopenia or to counterregulatory hormones that are released in response to increased discharge of the sympathetic nervous system. Signs of neuroglycopenia include lethargy, ataxia, collapse, and seizures. Catecholamines released in response to hypoglycemia can cause behavioral changes, muscle fasciculations, and hunger.

Insulinomas most commonly affect middle-aged to older dogs with no sex predilection. Unlike in humans, the majority of insulinomas in dogs are malignant, with up to 50% or more of affected dogs having metastasis at the time of diagnosis. Metastasis to the regional lymph nodes, liver, and mesentery is most common. Surgical excision is the recommended treatment for insulinoma. Dogs with tumors confined to the pancreas (stage I) or to the pancreas and regional nodes (stage II) have a median survival of approximately 1.5 years, while dogs that have metastasis beyond the nodes (stage III) have a median survival of less than 6 months. There are only five reported cases of insulinoma in cats.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition
No sex predilection has been identified.

Age Predisposition
Insulinoma is a disease of middle-aged to older dogs, with the mean age of affected dogs being 8.9 years (range: 3 to 15 years).

Breed Predisposition
Large-breed dogs, including golden and Labrador retrievers, German shepherds, standard poodles, and Irish setters, appear to be overrepresented.

Owner Observations
Hunger, behavior changes, muscle fasciculations, weakness, ataxia, or seizures can be seen and are often exacerbated by exercise and/or fasting. Eating can also result in clinical signs because of excessive insulin release.

Other Historical Considerations/Predispositions
Younger dogs with insulinoma appear to be at increased risk for death.

Physical Examination Findings
- Physical examination findings in dogs with insulinoma are often unremarkable.
- Very rarely, dogs can present with seizures or in a comatose state.
- Very rarely, dogs can present with peripheral neuropathy.
Laboratory Findings

- Fasting hypoglycemia (<60 mg/dl) is the only consistent laboratory abnormality.
- Whipple's triad should be established to document a relationship between the hypoglycemia and clinical signs:
  - Hypoglycemia
  - Clinical signs of hypoglycemia
  - Resolution of clinical signs of hypoglycemia following administration of dextrose
- A presumptive diagnosis of insulinoma is made based on concurrent low blood glucose and normal or elevated insulin levels:
  - To appropriately collect the insulin–glucose pair, the patient must be fasted and kept off intravenous dextrose.
  - The blood glucose level should be monitored every 30 to 60 minutes until it falls below 60 mg/dL, at which point serum should be drawn for insulin levels.
  - Because the insulin level should be subnormal in a healthy dog with hypoglycemia, any insulin value not below the reference range is considered abnormal.
  - Insulin:glucose ratios and amended insulin:glucose ratios have been described, although these tests do not offer any advantage over the insulin–glucose pair and are more cumbersome to perform.
- Complete blood count, serum chemistry panel, and urinalysis should be performed to rule out other causes of hypoglycemia.
- Occasionally, dogs with insulinoma have mild liver enzyme abnormalities.

Other Diagnostic Findings

- Thoracic and abdominal radiography should be performed to rule out other causes of hypoglycemia but typically these tests do not reveal significant abnormalities with insulinomas.
- Abdominal ultrasonography may add useful information regarding the staging of insulinoma. While only about 30% of insulinomas can be detected, ultrasonography may aid in the assessment of metastases to the liver or lymph nodes.
- Several provocative tests have been described for the diagnosis of insulinoma, including:
  - Glucose tolerance test
  - Tolbutamidre tolerance test
  - Epinephrine stimulation test
  - Calcium infusion test
  However, none of these tests is as sensitive as the insulin–glucose pair.
- Serum glycosylated hemoglobin levels have also been assessed in insulinoma patients with variable results.
- Several intraoperative tests have been described to help localize the nodules:
  - Radiolabeled octreotide has been used experimentally in dogs. Octreotide binds to somatostatin receptors and appears useful in dogs to detect primary and metastatic nodules in insulinomas that contain somatostatin receptors.
  - Intraoperative ultrasonography of the pancreas appears to be an extremely sensitive method of detecting nodules in humans and may be of value in detecting canine insulinomas that are not clearly visible.

Summary of Diagnostic Criteria

- The typical presentation for a dog with insulinoma is a large-breed dog with a history of weakness, ataxia, or seizures, signs that may be exacerbated with exercise or fasting.
- Physical examination findings are often within normal limits.
- The most consistent laboratory abnormality is a fasting hypoglycemia.
- Presumptive diagnosis is made with an abnormal insulin–glucose pair, with normal to elevated insulin levels in the face of low glucose levels.
- Abdominal ultrasonography may be useful to detect nodules in the pancreas as well as metastatic disease in the abdomen. Intraoperative ultrasonography may be useful if nodules cannot be detected by visual inspection. Additional diagnostic tests may help support the diagnosis of insulinoma but typically are not as sensitive as the insulin–glucose pair and abdominal ultrasonography.

Differential Diagnosis

Differentials for hypoglycemia other than insulinoma include:

- Laboratory error
- Liver disease, shunt, or congenital abnormalities
- Sepsis
- Neoplasia (i.e., gastrointestinal, splenic, and hepatic leiomyosarcoma and other liver tumors)
- Addison's disease
- Excess insulin administration
- Hunting dog hypoglycemia
- Polycythemia
- Ethylene glycol toxicity

TREATMENT RECOMMENDATIONS

Initial Treatment

If emergency treatment is required to control hypoglycemia, an intravenous dextrose bolus of 0.5 g/kg should be administered. The concentration should be diluted to 20% or less if it is to be administered through a peripheral vein. The patient should then be maintained on a 2.5% to 10% dextrose infusion, with the intent of alleviating clinical signs rather than restoring euglycemia. If neurologic signs persist after dextrose infusion, the patient should be treated for cerebral edema with dexamethasone (2 mg/kg IV) or mannitol (0.5 g/kg IV) over 20 minutes. Sometimes hypoglycemia is refractory to treatment because the administration of dextrose solutions stimulates insulin release and rebound hypoglycemia. A glucagon continuous-rate infusion is indicated in patients that are nonresponsive to dextrose solutions. One milligram of glucagon is added to 1 L
of 0.9% NaCl to make a 1,000-ng/ml solution. A loading dose of 50 ng/ml is given followed by a continuous-rate infusion of 10 to 15 ng/kg/min, up to 40 ng/kg/min, as needed to maintain euglycemia. Persistent seizures may require anticonvulsant medication.

Surgery is the initial treatment of choice for insulinoma. Blood glucose must be normalized before, during, and after surgery. This is important because palpation of the nodules during surgery can result in insulin release. Palpation allows localization of the nodules in the majority of cases. Insulinomas tend to occur in the right and left lobes of the pancreas with equal frequency. Nondiscriminatory removal of pancreatic tissue is not recommended. Removal of the nodules can be performed by nodulectomy or partial or total pancreatectomy. Exploration with biopsy of suspicious areas in the abdomen should be performed. Metastasis has been reported in 36% to 51% of dogs at the time of initial surgery. Metastasis is most common to the liver and lymph nodes but has also been reported in the intestines, mesentery, spleen, and kidneys. Metastatic disease should be debulked as much as possible, as this may provide significant improvement in clinical signs. Resection of the insulinoma may result in postoperative hyperglycemia because of atrophy of normal β cells and inadequate normal insulin production.

**Alternative/Optional Treatments/Therapy**

Symptomatic therapy is warranted if surgery is not performed or if clinical signs are not controlled with surgery.

**Dietary Modification**

Dietary modification is the most important initial therapy. Frequent (four to six times per day) small meals consisting of foods high in fat, protein, and complex carbohydrates is recommended. It is also recommended that exercise be restricted.

**Medical Therapy (Table 1)**

- If dietary modification and exercise restriction do not control hypoglycemia, prednisone (0.25 mg/kg bid) should be administered. Prednisone has effects that antagonize insulin action and help promote gluconeogenesis and glycogenolysis.
- When prednisone ceases to work, the benzothiadiazide diazoxide can be used, initially at 5 mg/kg bid. Up to 30 mg/kg twice daily can be administered. Diazoxide decreases insulin release from β cells. Side effects may include anorexia, vomiting, diarrhea, myelosuppression, pancreatitis, and diabetes mellitus.
- Hydrochlorothiazide, a thiazide diuretic, can be used at 2 to 4 mg/kg/day to potentiate the effects of diazoxide.
- Octreotide, a somatostatin analogue, can be used at 10 to 20 µg SC bid–tid instead of diazoxide if side effects are severe. Octreotide binds to somatostatin receptors and inhibits insulin synthesis and secretion. No significant adverse effects have been reported.
- Calcium-channel blockers (e.g., verapamil, diltiazem) may be useful by inhibiting insulin release. Efficacy has not been completely assessed in dogs.
- β-blockers (e.g., propranolol) inhibit β-adrenergic–mediated insulin secretion. They have also not been fully evaluated in dogs.

**Chemotherapy**

- Alloxan is a chemotherapy agent that is directly toxic to pancreatic β cells. Alloxan has been administered at 65 mg/kg IV with variable results in some dogs. Adverse effects include nephrotoxicity and acute respiratory distress syndrome.
- Streptozotocin is a nitrosourea alkylating agent that is also directly toxic to pancreatic β cells. Streptozotocin has been administered at a dose of 500 mg/m² IV q3wk with some efficacy in 17 dogs with insulinoma. The major side effect of streptozotocin is dose-related nephrotoxicity, necessitating an

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**TABLE 1. Medical Therapy for Canine Insulinoma**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Prednisone</td>
<td>0.25 mg/kg bid</td>
<td>Antiinsulin effects, promotes gluconeogenesis and glycogenolysis</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>5 mg/kg bid initially, then up to 30 mg/kg bid</td>
<td>Decreases insulin release from β cells; stimulates epinephrine release, which promotes gluconeogenesis and glycogenolysis</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>2–4 mg/kg q24h</td>
<td>Potentiates the effects of diazoxide</td>
</tr>
<tr>
<td>Octreotide</td>
<td>10–20 µg SC bid–tid</td>
<td>Inhibits insulin synthesis and secretion by binding to and activating somatostatin receptors</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Loading dose and continuous-rate infusion (see Treatment Recommendations section)</td>
<td>Antiinsulin effects, promotes gluconeogenesis and glycogenolysis</td>
</tr>
<tr>
<td>Alloxan</td>
<td>65 mg/kg IV</td>
<td>Cytotoxic to β cells</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>500 mg/m² IV (CAUTION: must use saline diuresis)</td>
<td>Cytotoxic to β cells</td>
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aggressive diuresis protocol. The diuresis protocol consists of administering the following:
— 0.9% NaCl at a rate of 18.3 ml/kg/hr IV for 3 hours
— Streptozotocin solution diluted to an appropriate volume to allow administration at 18.3 ml/kg/hr for 2 hours
— 2 additional hours of 0.9% NaCl diuresis at 18.3 ml/kg/hr.
Other side effects of streptozotocin include vomiting and hepatic toxicity. Antiemetics should be used in during administration of streptozotocin.

Patient Monitoring
• Glucose levels should be monitored frequently.
• Insulin–glucose pairs should be monitored periodically.
• To monitor recurrence or metastasis, abdominal ultrasonography should be performed every 3 months or more frequently if clinical signs or hypoglycemia occurs. If clinical signs of hypoglycemia occur, the animal should see a veterinarian immediately.

Home Management
Owners should be instructed to monitor for signs of hypoglycemia. The pet should be fed a small meal if signs of weakness occur. Corn syrup should be applied to the gums and medical attention sought immediately if more severe signs (e.g., seizures) occur.

Milestones/Recovery Time Frames
• If surgery is successful, euglycemia or occasionally hyperglycemia occurs almost immediately. Hyperglycemia, if it occurs, is usually transient.
• With either surgical or medical therapy, clinical signs resolve once the hypoglycemia is corrected.

Treatment Contraindications
Dogs with insulinomas should not be fed simple sugars or semi-moist dog food, as these can cause an increase in insulin response due to postprandial hyperglycemia.

PROGNOSIS
Remission and survival in dogs with insulinoma following surgery depend on the clinical stage at the time of diagnosis (Table 2). The median survival time of all affected dogs is approximately 12 months.

Favorable Criteria
• Dogs with tumors confined to the pancreas (stage I) have a longer remission time (defined as the period of euglycemia) than dogs whose tumors have metastasized. Dogs with stage I disease have a median remission time of approximately 14 months versus approximately 1 month for stage II or III dogs.
• Dogs with tumors confined to the pancreas (stage I) or to the pancreas and regional nodes (stage II) have a longer survival time than dogs with tumors that are metastatic beyond the nodes (stage III). Dogs with stage I or II disease have a median survival of approximately 1.5 years, while dogs with stage III disease have a median survival of 6 months or less.
• Partial pancreatectomy yields longer survival times than nodulectomy.

Unfavorable Criteria
• Total pancreatectomy is associated with high morbidity and mortality.
• Tumors in the body of the pancreas are more difficult to remove than tumors in the limbs of the pancreas.
• Persistent postoperative hypoglycemia indicates that a residual tumor (either primary or metastatic) exists.

RECOMMENDED READING

TABLE 2. Clinical Staging System for Canine Insulinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Insulinoma confined to the pancreas</td>
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<tr>
<td>II</td>
<td>Insulinoma in the pancreas and regional lymph nodes</td>
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<tr>
<td>III</td>
<td>Insulinoma with distant metastases</td>
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