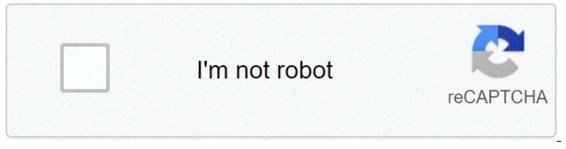

I am not robot!

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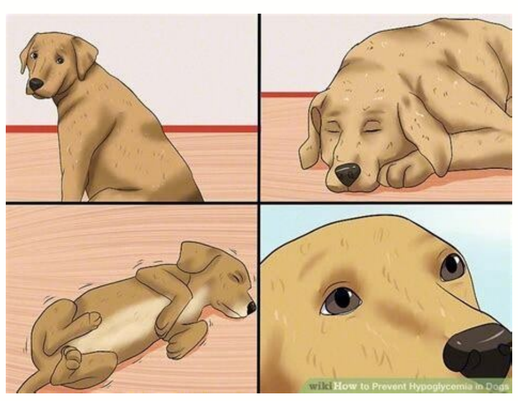

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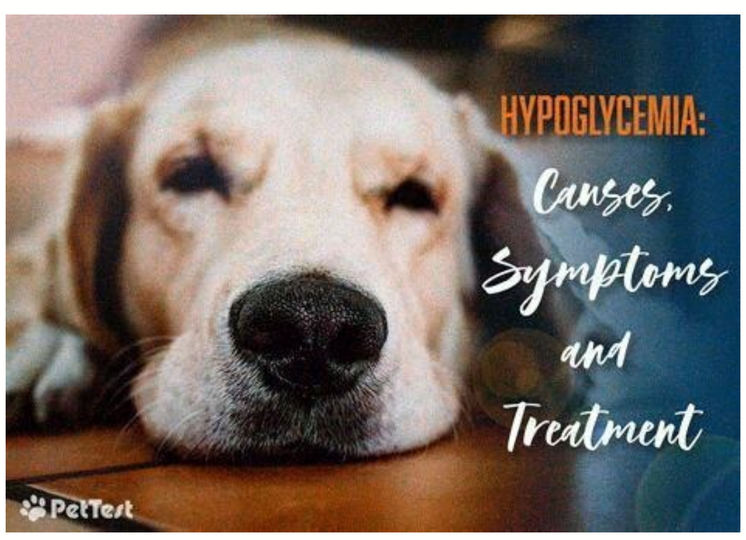

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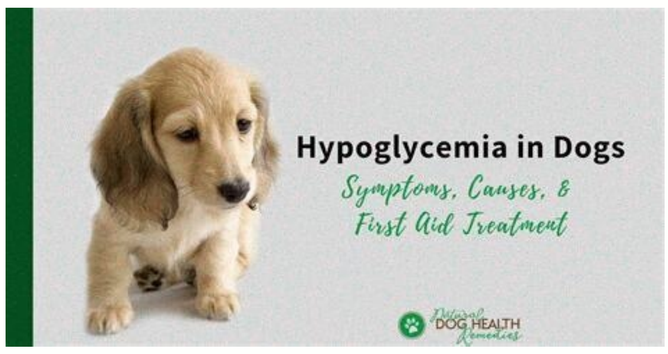

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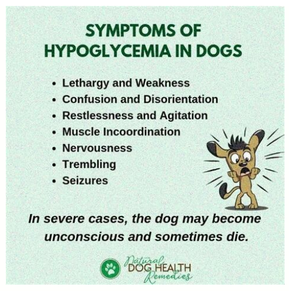

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[PubMed] [Google Scholar]Page 2Causes of hypoglycemia in the dog broadly divided by the presence or absence of an underlying disease resulting in hypoglycemia (1,6).Physiological causes of hypoglycemiaChief mechanism or mechanismsExtreme exercise (e.g., hunting dog hypoglycemia)Excess glucose utilization and inadequate glycogen storesNeonatal/juvenile or toy breed juvenile hypoglycemiaInadequate glycogen stores, limited fat and muscle massMalnutrition/starvationInadequate intake and depletion of glycogen storesDrug and toxin associated causes such as iatrogenic insulin overdose, xylitol toxicity, oral hypoglycemic agents (usually sulfonylureas), beta blockersExcess glucose utilization due to hypersecretion of insulin and increased tissue sensitivity to insulin. Beta blockers via suspected interference of counter- regulatory mechanisms Pathological causes of hypoglycemia Severe hepatic disease such as hepatitis, cirrhosis, neoplasia, amyloidosis, hepatotoxinsDecreased hepatic gluconeogenesisCongenital portosystemic shuntDecreased hepatic gluconeogenesisHypoadrenocorticismDecreased glucose production from lack of a counter-regulatory hormone (i.e., cortisol)HypopituitarismDecreased glucose production from lack of a counter-regulatory hormone (i.e., growth hormone or adrenocorticotropic hormone)InsulinomaExcess glucose utilization due to hypersecretion of insulinIslet cell hyperplasiaExcess glucose utilization due to hypersecretion of insulinExtra-pancreatic tumors (e.g., hepatocellular carcinoma, hepatoma, leiomyosarcoma, leiomyoma)Increased glucose utilization by the tumor but also due to secretion of insulin analoguesChronic renal failureDecreased hepatic gluconeogenesisPancreatitisUnknownInfection (e.g., sepsis, severe canine babesiosis)Decreased hepatic glycogenesis and increased glucose utilizationGlycogen storage diseaseDeficiency of enzymes required for glycogen conversion Artifactual/spuriousLaboratory error from improper sample handling or submission, use of a human glucometer, leukemia/polycythemia vera A 6-year-old male, neutered shih tzu cross dog was presented to the referring veterinarian with a history of acute onset ataxia and anorexia of 2 d duration. On physical examination, the dog was depressed, ataxic, and disoriented, but otherwise normal with no neurologic deficits. Initial bloodwork revealed a marked fasting hypoglycemia of 1.6 mmol/L [reference interval (RI): 3.3–6.1 mmol/L]. Other abnormalities included mildly increased albumin (43 g/L; RI: 26–36 g/L), mildly increased amylase (1273 U/L; RI: 138–970 U/L) and lipase (683 U/L; RI: 0–600 U/L), and mildly decreased urea (1.78 mmol/L; RI: 2.14–8.56 mmol/L) and creatinine (44.2 µmol/L; RI: 61.9–114.9 µmol/L). Pre- and post-prandial bile acids were mildly increased (pre-prandial 16.0 µmol/L; RI: 0–15.0 µmol/L; post-prandial 28.5 µmol/L; RI: 0–22.0 µmol/L). The complete blood (cell) count (CBC) revealed only a mild stress lymphopenia. The urine specific gravity was 1.004, and the urinalysis data were unremarkable. Thoracic and abdominal radiographic findings were unremarkable.Hypoglycemia is defined as a blood glucose concentration of < 3.3 mmol/L (1). An initial finding of hypoglycemia should always be confirmed before beginning to work up the problem. Artifactual hypoglycemia is common when there has been a delay in the separation of serum from cells because erythrocytes and leukocytes continue to utilize glucose (in vitro glycolysis). The glucose concentration in whole blood may decrease by as much as 5% to 10% or 0.56 mmol/L per hour (1,2).Differential diagnoses for hypoglycemia in the dog are numerous (Table 1). In this dog, hepatic disease, sepsis, hypoadrenocorticism, beta-cell neoplasia, and extrapancreatic neoplasia were considered. Primary hepatic disease was considered unlikely since bile acids were only mildly increased and liver enzymes were within reference intervals. Sepsis was ruled out based on the lack of a neutrophilia or left shift, and hypoadrenocorticism was considered unlikely given the stress lymphopenia and absence of electrolyte abnormalities. A paired insulin and glucose test revealed markedly increased insulin (837 pmol/L; RI: 10–170 pmol/L) in the face of hypoglycemia (glucose 2.1 mmol/L; RI: 3.3–6.1 mmol/L), which greatly increased the suspicion of beta-cell neoplasia.Causes of fasting hypoglycemia in the dog (1–3)Causes CommonUncommonRareArtifact (delay in separation of serum)Nonpancreatic neoplasiaGlycogen storage diseaseNeonatal and juvenile hypoglycemiaGrowth hormone deficiencyHepatic disease (liver failure, vascular shunts)Pregnancy hypoglycemiaGlucagon deficiencyHunting dog hypoglycemiaStarvation and severe malnutritionSepsisIatrogenic (known diabetic)Severe polycythemiaHypoadrenocorticismToxinBeta-cell neoplasia (insulinoma)Renal failureCardiac failureAn abdominal ultrasound examination was performed with a Siemens G60-S Sonoline machine (Siemens Canada, Mississauga, Ontario) using a 7.5 MHz microconvex array transducer. The liver contained multiple hypoechoic nodules up to 10 mm in diameter with 1-mm wide echogenic margins (Figure 1). Multiple enlarged hypoechoic and plump abdominal lymph nodes were seen in the cranial abdomen.
The pancreas was hypoechoic and thickened up to 18-mm wide, irregular in margination with multiple ill-defined hypoechoic nodules diffused throughout the parenchyma (Figure 2).
The peripancreatic mesentery was increased in echogenicity, suggesting inflammation. The rest of the abdominal organs including the spleen, kidneys, gastrointestinal tract, and adrenal glands were sonographically within normal limits. Differential diagnoses based on the ultrasound findings included pancreatitis; pancreatic and hepatic nodular hyperplasia; exocrine or endocrine pancreatic neoplasia; and extrapancreatic neoplasia with metastasis to the liver, pancreas and regional lymph nodes. However, pancreatic beta-cell neoplasia with multiple metastatic sites was most consistent with the history of hypoglycemia and inappropriately increased insulin.Ultrasound-guided, fine-needle aspirates of the liver nodules and cranial abdominal lymph nodes were obtained and stained with DipQuick stain (Jorgensen Laboratories, Loveland, Colorado, USA). The dog did not remain cooperative for the pancreas to be safely aspirated. Aspirates from the liver were highly cellular and contained numerous clusters of 2 types of cells (Figure 3). There were several small clusters composed of uniform hepatocytes.
Most of the clusters were larger and appeared to be composed of free nuclei embedded in basophilic cytoplasm. This appearance is typical of neuroendocrine tissue. Nuclei were round to oval, with a finely stippled chromatin pattern, and the cytoplasm was deeply basophilic and often contained clear vacuoles. There were few cells with intact cytoplasmic borders. The cells displayed moderate anisokaryosis and occasionally had prominent nucleoli. There were few binucleate cells. Aspirates from the lymph nodes contained numerous similar clusters of cells typical of neuroendocrine tissue. The cytologic interpretation was metastatic neuroendocrine neoplasia, most likely beta-cell neoplasia.Cytologic appearance of the fine-needle aspirate from hepatic nodules.
A) There are several clusters of hepatocytes (black arrow) and neoplastic neuroendocrine cells (white arrows). DipQuick, x50 objective. B) Note the appearance of free nuclei embedded in the cytoplasm without visible cell borders. The cells display only mild anisokaryosis despite being metastatic lesions. DipQuick, × 100 objective.Functional beta-cell tumors, often called insulinomas, arise from the neoplastic transformation of beta cells within the endocrine pancreas. Beta cells comprise 60% to 70% of pancreatic islet cells (3). Neoplastic beta cells secrete a variety of hormones in addition to insulin, including glucagon, serotonin, gastrin, somatostatin, and pancreatic polypeptide. However, insulin is secreted most commonly and is the cause of hypoglycemia and its resultant clinical signs, which may potentially mask clinical signs associated with secretion of the other hormones (1,4).The normal beta cell monitors blood glucose levels and secretes insulin when the blood glucose concentration exceeds 6.1 mmol/L (1). Insulin prevents the development of hyperglycemia by suppressing endogenous glucose production in hepatocytes via glycogenolysis and gluconeogenesis, and by stimulating glucose uptake and utilization by tissues, namely liver, muscle, and adipose tissue (2). When the blood glucose concentration falls below 3.3 mmol/L, normal insulin synthesis and secretion are inhibited. Neoplastic beta cells, however, autonomously secrete insulin despite declining blood glucose concentrations, often resulting in profound hypoglycemia. They may also secrete excessive amounts of insulin in response to increased blood glucose concentrations, which can result in clinical signs of hypoglycemia after eating (1). Insulin-induced hypoglycemia is counteracted by increased secretion of glucose-raising hormones, including glucagon, epinephrine, growth hormone, and cortisol (1). However, the net effect of insulin-secreting tumors is hypoglycemia because of increased tissue utilization of glucose.The clinical signs of hypoglycemia are the result of both decreased glucose supply to the brain and stimulation of the counter-regulatory sympathoadrenal system (1). The CNS is dependent on a continuous supply of glucose from the blood. When blood glucose concentrations decrease below a critical level, cerebral oxidation decreases, and neuroglycopenic signs such as lethargy, weakness, ataxia, altered mentation, seizures, and coma result (5). Counter-regulatory stimulation of the sympathoadrenal system in response to hypoglycemia results in the release of catecholamines, causing muscle tremors, nervousness, restlessness, and hunger. Clinical signs are often seen after fasting, exercise, excitement, and eating, and are rapidly alleviated by the administration of glucose. Clinical signs are typically episodic due to the counter-regulatory mechanisms that compensate for decreased blood glucose. Seizures occur when initial mechanisms are inadequate to raise the blood glucose concentration, and may stimulate further secretion of glucose-raising hormones. The severity of the clinical signs depends on the duration and severity of hypoglycemia.
Repeated episodes of severe and prolonged hypoglycemia may lead to coma and death, with irreversible neuronal degeneration throughout the brain (5).Clinical diagnosis of beta-cell neoplasia relies on demonstration of inappropriate serum insulin levels in the face of fasting hypoglycemia and the presence of a pancreatic mass (1,6). Dogs with beta-cell tumors are typically middle-aged to old, and large breeds such as retrievers and German shepherds are over-represented. Dogs are presented with a history of clinical signs related to hypoglycemia. Physical examination findings and routine bloodwork and urinalysis are usually unremarkable except for hypoglycemia, but are important in ruling out other conditions causing similar clinical signs. Persistent hypoglycemia should be confirmed. In some dogs, fasting and hourly evaluation of blood glucose concentration is needed to demonstrate hypoglycemia (1). A high normal or increased serum insulin concentration, typically > 71.7 pmol/L, in the face of hypoglycemia, especially serum glucose < 2.8 mmol/L, is highly supportive of the presence of a beta-cell tumor (1). In 3 studies, no dogs with insulinomas had serum insulin concentrations below reference intervals, and between 56% and 83% of dogs had serum insulin concentrations greater than the high end of the reference interval (215 pmol/L) (6–8). Sepsis and nonpancreatic neoplasia can also occasionally result in increased serum insulin in the face of hypoglycemia (3).Various insulin:glucose ratios have been developed to aid the diagnosis of insulin-secreting tumors; however, conditions other than insulinomas may yield increased ratios and dogs with beta-cell tumors may have normal insulin:glucose ratios (6,7,9). Feldman and Nelson (1) recommend interpreting the serum insulin concentration during hypoglycemia in conjunction with the dog’s history, physical findings, and clinical pathologic findings, rather than relying on an increased insulin:glucose ratio. Other diagnostic tests such as ultrasonography, cytology, and histopathology are also useful in confirming the diagnosis.Abdominal radiographs are generally not helpful in identifying beta-cell tumors because of the small size of these masses and border-effacement from the surrounding soft tissues of the cranial abdomen (1,8). Thoracic radiographs often do not demonstrate metastatic disease because beta-cell tumors rarely metastasize to the lungs until late in the disease. Abdominal ultrasound examination can be helpful in confirming a diagnosis of beta-cell neoplasia if a mass in the pancreas is detected. Nodules in the peripancreatic omentum or liver and enlarged regional lymph nodes suggest metastatic disease. However, failure to identify a pancreatic mass does not rule out beta-cell neoplasia. In one study, only 32% of dogs with histologically confirmed beta-cell tumors had evidence of a pancreatic mass on ultrasound evaluation (1). Exploratory surgery may yield a small mass in these cases. Ultrasound-guided fine-needle aspirates or biopsies of any mass lesions may also be obtained during ultrasonographic evaluation.
Other diagnostic imaging techniques such as somatostatin receptor nuclear scintigraphy using indium-111 pentetreotide (10); computed tomography; and single-photon emission computed tomography (SPECT) positron emission tomography have been used in the diagnosis of beta-cell neoplasia. The diagnostic accuracy of these techniques remains largely undetermined and they are not widely available to the general practitioner (11).Cytologic evaluation of aspirates from beta-cell tumors reveals clusters of cells typical of neuroendocrine tissue, which has the appearance of free nuclei embedded in cytoplasm without visible cell borders (12). Other neuroendocrine tumors, for example gastrinomas, have a similar cytologic appearance, but do not cause hypoglycemia. If tissue is obtained, immunohistochemistry can be used to confirm that the neuroendocrine cells are producing insulin (4) (Figure 4). Anaplastic features are often mild or inconsistent, despite the fact that most beta-cell tumors in the dog are malignant (12). Microscopic evaluation is not reliable in determining malignancy, which should be based on the presence or absence of metastasis and the clinical course of the disease (6). Cytology of suspected metastatic sites may confirm the presence of metastasis. Cytology can also be useful in ruling out non-beta-cell neoplasia. Tumors such as leiomyoma, leiomyosarcoma, hepatocellular carcinoma, and various other types of tumor have been associated with hypoglycemia (1).Histologic section of a pancreatic mass removed from a 10-year-old male, castrated golden retriever diagnosed with a beta-cell carcinoma. The section has been stained with guinea pig anti-insulin antibodies using the avidin-biotin-complex peroxidase method. The brown staining within neoplastic cells indicates the presence of insulin.
Bar = 100 µm. (Courtesy of Andy Allen, Western College of Veterinary Medicine).The long-term prognosis for a dog with beta-cell neoplasia is guarded to poor due to the high likelihood of malignancy (1). Metastasis is seen at the time of surgical intervention in 45% of dogs, most often to the regional lymph nodes and liver, but also to the duodenum, mesentery, and omentum (6).
Even dogs with an apparently single pancreatic mass that is completely resected often have recurrent hypoglycemia months later (1). Dogs with tumors confined to the pancreas (stage I) or with metastasis to regional lymph nodes (stage II) have a median survival time of approximately 18 mo after surgery, whereas dogs with distant metastasis (stage III) have a median survival time of less than 6 mo after surgery (6). Younger age at diagnosis and higher preoperative serum insulin concentrations are poor prognostic indicators associated with significantly shorter survival times (6).It is difficult to compare medical versus surgical management of dogs with beta-cell neoplasia, as medical management is often pursued in dogs that have extensive metastatic disease and are not candidates for surgical management. Medical management of dogs with beta-cell neoplasia involves managing chronic hypoglycemia through nonspecific antihormonal therapy, such as frequent feedings and glucocorticoids (1). Various anti-insulinogenic drugs such as diazoxide, octreotide, streptozocin, and alloxan may occasionally be used. The eventual development of uncontrollable hypoglycemia leads to death or euthanasia (1).This dog’s ataxia resolved within 30 min with intravenous dextrose therapy and his blood glucose remained stable with multiple frequent feedings once the dextrose was discontinued. Unfortunately, after being discharged he once again became anorexic and ataxic.
With the guarded to poor prognosis and presence of metastatic disease, rather than pursue assisted feeding or appetite stimulant, the owners elected humane euthanasia. A postmortem examination was not performed.This case is a classic example of insulin-secreting beta-cell neoplasia in the dog. The dog was presented with ataxia and disorientation, but was otherwise normal. He had markedly increased serum insulin in the face of hypoglycemia. Abdominal radiographs did not demonstrate a mass. Visualization and aspiration of the lesions with ultrasound allowed cytologic confirmation of the presence of metastatic neuroendocrine tissue.1. Feldman EC, Nelson RW. Canine and Feline Endocrinology and Reproduction. 3rd ed. St Louis, Missouri: Saunders; 2004. pp.
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