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Canine Insulinoma

by

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INTRODUCTION

Canine insulinoma is the neoplastic growth of the Beta cells of the pancreas. In man 90% of the growths are found to be benign while in the dog reports say 69-81% of the growths are malignant (2,7). A malignant canine insulinoma denotes a functional neoplasm secreting excessive amounts of insulin or what some authors term inappropriate release of insulin (1). Cause of death can be from “irreversible hypoglycemic brain damage” as well as euthanasia following unsuccessful management of a vague neurological disorder or surgical discovery of malignancy and metastasis. Presenting signs are often vaguely neurological as well as intermittent, leading to a slow, prolonged diagnostic course which decreases the prognosis accordingly. Canine insulinoma is often seen in older dogs, without predisposition to sex. Some authors report seeing canine insulinoma over-represented in the Boxer and Terrier breeds (2,3,13).

PATHOGENESIS AND CLINICAL SIGNS

Early in the course of the disease, the unregulated neoplastic outpouring of insulin has the effect of lowering blood glucose as well as inhibiting hepatic gluconeogenesis. Clinical signs may or may not be present depending on the rate of decline of blood glucose. Later in the course of the disease, as the blood glucose begins to fall more rapidly, the pituitary-adrenal axis responds to counter the insulin effects with STH, glucocorticoids, glucagon, epinephrine, and norepinephrine. As the disease progresses and the neoplasm increases in size, the pituitary-adrenal axis’ counter measures are exhausted and the clinical signs once again appear more prevalent (14). The intermittancy of the clinical signs makes early diagnosis very difficult as neurological exams seldom uncover deficits. As can be seen, it is not until late in the course of the neoplasia, when the prognosis is poor, that the clinical signs become more consistent and severe.

Clinical signs are directly related to hypoglycemia. It is not the low level of the blood glucose which causes the signs but the rate of decrease of blood glucose (7,12). Many dogs develop a tolerance to low levels of blood glucose and can remain outwardly normal with blood glucose levels as low as 30 mg% or less (5). Because the brain does not depend on insulin to supply it with glucose, the over supply of insulin leads to over supply of glucose to most tissues excluding the brain. While the presented animal is usually polyphagic and in good flesh or obese, the brain is literally starving to death. Most authors agree that generalized epileptiform seizures are seen in about 50% of the cases. If the clinician is fortunate enough to observe a seizure, it can be noted that the hypoglycemic seizure does not closely follow the preictal, ictal, and postictal phases of epileptic seizures. If the owners are questioned closely or the clinician is observant certain stimuli can be found which precede most onsets of clinical signs. These stimuli can be causes of glucose utilization such as excitement, exercise, or fasting, or they can be a cause...
of insulin release, such as eating. Other signs commonly occurring are generalized muscle weakness, paraparesis, generalized muscle twitching, disorientation, hysteria, stupor, coma, opisthotonus, and polyphagia. It is not uncommon for the animal to seem perfectly normal between bouts of clinical signs.

**DIAGNOSIS**

At one time, completion of Whipple's Triad was considered diagnostic for canine insulinoma. Whipple's Triad consists of a neurological disorder, hypoglycemia, and reversal of signs upon administration of IV glucose (12). It is now realized that many disorders will respond in a similar manner. These include hypoadrenalism, hypopituitarism, hepatic lipidosis, hepatic glycogen storage diseases, hepatic cirrhosis, inanition, cachexia, and even some large mesodermal extrapancreatic tumors. The extrapancreatic tumors are thought to utilize glucose at a rate faster than can be maintained by gluconeogenesis, and have been seen as metastatic mammary carcinomas and primary pulmonary carcinomas (7,12). Other conditions, not specifically related to blood glucose levels, that can easily be confused with the clinical signs of canine insulinoma are idiopathic epilepsy, brain tumor, lead poisoning, canine distemper, and organic brain lesions, as well as lumbar and cervical intervertebral disc diseases (2,7,14).

Hypoglycemia as determined by a fasting blood glucose test (using the orthotoludine method) should make the clinician suspicious of canine insulinoma. Ideally, the dog should be in a calm, quiet, relaxed atmosphere when the blood sample is taken. Quite often the dog is profoundly hypoglycemic with blood glucose levels below 50 mg%. On the other hand, a normal blood glucose level after a 24 hr fast does not rule out canine insulinoma as sometimes a 48 hr fast is needed to demonstrate severe hypoglycemia (7). In practice 2-3 fasting blood glucose values less than 40-50 mg% would be justification to run or advise a glucagon tolerance test. Organic hypoglycemia must be differentiated from functional hypoglycemia, a condition sometimes found in hunting dogs and toy breeds. Functional hypoglycemia is the result of increased utilization of blood glucose due to chronic starvation, malabsorption, liver damage, poisons, deficient glycogen storage, or high carbohydrate diets and is characteristically temporary in nature. Often the animal is normal upon presentation to the clinician. Organic hypoglycemia finds its causes in over-treated diabetes mellitus, liver diseases, kidney disease, hypopituitarism, as well as canine insulinoma (5,14).

Many tests normally used to detect hypoinsulinism (diabetes mellitus) can also be used to indicate the hyperinsulinistic state. Various glucose tolerance tests fall into this category. Oral administration of glucose carries the variable of enteric absorption and blood flow. A high dose of glucose ($\approx$ g/lb) given IV would result in little rise in blood glucose from samples taken in the first few hours post injection in a canine insulinoma dog. As mentioned above, other hypoglycemic conditions may react in a similar manner. Because of the interdependency of endocrine and exocrine components of the pancreas, the high dose intravenous glucose tolerance test can be abnormal in cases of pancreatitis and pancreatic degeneration, as well as canine insulinoma (1).

Ideally, a clinician would like to take a blood sample and determine the level of insulin in the blood stream. This is possible using the immunoreactive insulin test. This test gives a quantitative insulin level, normal being about 20 uU/ml. Any value above 50-54 uU/ml is considered abnormal and diagnostic for canine insulinoma. However, this differs among private labs. Samples sent to labs should request a normal value and/or include blood from a normal dog. The drawback to this procedure is expense as well as the availability of facilities needed to run such a test. Few practices have sufficient volume to warrant such a clinical pathology lab. Often, though, clinicians can make arrangements with area hospitals to run this and similar tests. In some cases, the test is run through the attending veterinarian and in others, the client deals with the hospital who sends the results to the veterinarian and the bill to the client. The latter case seems to be easier for
the veterinarian, as well as cheaper for the client. Some tests must be disqualified on the basis of side effects or risks involved. Epinephrine response tests have been used by some to demonstrate canine insulinoma. Sympathetic side effects occurring during the test can be risky in critical cases. Tolbutamide, a hypoglycemic drug used in some human diabetics, causes a direct stimulation of the Beta cells to release insulin. This results in a profuse outpouring of insulin in insulinoma dogs lasting up to 18 hours. A profound hypoglycemia is possible and for that reason the test is seldom used. The risk here is too great for hypoglycemic convulsions, coma, and brain damage due to anoxia.

The test of choice for the clinician would include such qualities as ease of administration, little risk to the patient, and diagnostic results. The glucagon tolerance test seems to fulfill these requirements better than any other test and still be economical. Glucagon acts to stimulate hepatic glycogenolysis while directly stimulating insulin release from the B cells of the pancreas. This results in a sharp response with less risk of hypoglycemic convulsions and coma.

After a 12 hr fast, blood is taken for a preinjection blood glucose level. Glucagon is then administered at the rate of 0.03 mg/kg given intravenously. Blood is then drawn at 5, 15, 30, 45, 60, 90, 120, and 180 minutes after the glucagon injection for blood glucose level determinations (7, 8). Some authors advocate taking blood at 1 and 3 minutes as well to detect a slight dip in levels before the large rise. Blood glucose determinations should be run as samples are taken or at least spun down and the serum removed. The reason for this being the blood glucose levels will decrease at about the rate of 10% per hour due to utilization of glucose by white blood cells (5, 16).

A dog with normally responsive Beta cells should have a high blood glucose level for more than 2 hrs, then slowly decline to normal levels. A dog with an insulinoma will respond with a neoplastic outpouring of insulin, dropping the blood glucose level below normal in less than 2 hrs and often leading to a hypoglycemic state. While the glucagon tolerance test is not as risky as the tolbutamide test, glucose should always be kept ready for intravenous administration in case of hypoglycemic convulsions or coma. To aid in the evaluation of the glucagon tolerance test, a normal dog can be tested simultaneously to emphasize the difference in response of the normal versus the neoplastic Beta cells.

TREATMENT

Treatment of canine insulinoma is often discouraging. Due to the difficulty in rapid diagnosis of the condition, it is often too late in the course of the neoplastic process for simple excision or successful long term medical treatment. In that light, accurate diagnosis is directed toward saving the owner unneeded expenses rather than saving the dog.

Dogs that are seen by the clinician in a seizure or hypoglycemic coma should be treated with IV 50% dextrose given to effect (7, 14). In an emergency or in the owner's home, table sugar can be used at the rate of 1 tablespoon/10 lb given orally (11). Oral treatment is probably only safe in a dog showing a weakness rather than in a seizure or comatose state, as compromised swallowing reflexes would necessitate the expertise of passing a stomach tube for sugar administration.

Long term medical treatment of insulinoma is only palliative and will very rarely result in any sort of cure. It consists basically of methods of avoiding or decreasing the stimulation of insulin release. The diet is gradually changed over to a high protein, low carbohydrate ration. Smalls amounts of food should be given frequently at least four times daily (3, 7, 11, 14). At times of exercise, high carbohydrate snacks should be given to counter balance glucose utilization (11). It is essential that the client be well aware of the stimulants of insulin release so that the risk of unnecessary seizures is decreased. Glucocorticoid administration is also advisable to enhance gluconeogenesis and glycogen storage in the liver. Glucocorticoids are also responsible for some minor amount of peripheral insulin antagonism (14). Anti-B cell drugs such as alloxin and streptozotocin are not only difficult to
obtain but have not been consistently successful. Side effects to these drugs often discourage their use (3,7,14). There is some discussion that alloxin may only be effective against normal Beta cells rather than neoplastic Beta cells (2).

Long term medical treatment can often be successful in prolonging the life of a canine insulinoma patient. Some thought must be given to the quality of life of the patient. The idea of euthanizing a dog that is normal most of the time can be as unsettling for the owner as can watching an old friend going steadily downhill. Obviously, the most satisfactory results lie somewhere in the middle when the seizures reach a frequency or severity intolerable to the owner.

Surgical correction of insulinoma by complete excision of the neoplastic mass must be accomplished early in the course of the neoplasia as the majority readily metastasize. Metastatic lesions can be found in the regional lymph nodes, liver, mesentery and omentum. To complicate matters, some forms of canine insulinomas are diffusely spread throughout the pancreas and are difficult to visualize at surgery. Some authors report a higher incidence of neoplasia in the right or duodenal lobe of the pancreas while others insist that no such prevalence exists (2,7,13). The next logical step at surgery would be to remove the entire pancreas. Before this is done it is best to consider having the owner aware of the cost and trouble of maintaining a dog on insulin and pancreatic enzymes for life. The success of this procedure is dependent on the lack of metastasis. Persistent post-operative hypoglycemia can be considered indicative of metastatic lesions (13).

Because idiopathic hyperthermia has been encountered postoperatively, it is advisable to administer preoperative glucocorticoids prophylactically (3,7,13). Also, because surgical handling of the pancreas is associated with insulin release, 10% dextrose fluids should be ready to administer during surgery (2,3,7). If the whole pancreas is not removed, it is a good idea to treat postoperatively for pancreatitis, as signs attributable to this are often seen after surgical manipulation of the organ (2,3,7). Postoperative monitoring can be as extensive as daily levels of blood glucose, serum potassium, amylase, lipase, and BUN. These can later be tapered down to monthly determinations of fasting blood glucose if the patient recovers uneventfully (2,7).

CASE REPORTS

Case One

Trixi, a female, eleven year old, terrier type dog was admitted to Stange Memorial Clinic (SMC) with a two year history of seizures. The seizures had increased in frequency and were now a daily occurrence. Anti-convulsive drugs (Myelens and Dilantin) prescribed by the referring veterinarian seemed to decrease the severity of the seizures but did not eliminate them. The seizures, when characterized by the owner, did not fit into an epileptic pattern. Trixi was described as becoming drunk-like, staggering, falling, becoming dyspneic, and showing some muscle rigidity. The owners felt that Trixi would often turn to the right before falling, sometimes crying out or vomiting first.

Physical and neurologic exams revealed that Trixi was depressed and atactic; anticonvulsive medication (Primidone) was stopped to prevent interference with future neurologic exams. No neurological deficits or muscle twitches were detected. Trixi's mental state was characterized as scared and timid. Blood drawn for analysis indicated hypoglycemia (48 mg%) and, although Trixi had been anorexic for three previous days, a future rerun of parameters was scheduled. Trixi's appetite improved and blood was taken for another analysis. At this time, the blood glucose level was severely hypoglycemic (21 mg%) and a glucagon tolerance test was scheduled for the following day. Throughout Trixi's hospital confinement the only known seizure occurred when the owners first left. Clinicians viewing the seizure felt that it did not fit an epileptic pattern.

Canine insulinoma was diagnosed from the results of the glucagon tolerance test and the owners elected surgery. Prognosis for a surgical cure was poor due to the extended duration of clinical signs (2 yrs) and the chance for metastasis. Preoperative
procaine penicillin and dexamethasone (Azium®) were given the day before surgery. Upon opening the abdominal cavity and locating the pancreas, the neoplasm was found to be metastasized to the liver, omentum, and lymph nodes. The owners then gave permission for euthanasia. Because the owners wanted the body, only a biopsy was taken for histiopathologic study. The study was consistent with gross observations.

Case Two

Missy, a female, six year old, spaniel type dog was admitted to SMC with the complaint of periodic fainting, ataxia, and urinary incontinence. The owners described three to four “spells” a day of aimless walking and periods of hyperactivity.

Blood analysis revealed a blood glucose level of 24 mg%. This low blood glucose level was in the absence of any “spells.” Results of a glucagon tolerance test were diagnostic for canine insulinoma and the owners elected euthanasia. Blood taken prior to euthanasia was sent to a private laboratory for an immunoreactive insulin test to determine the actual level of insulin in the blood stream. The level was reported to be 30 micro units/ml, whereas 4 micro units/ml is considered normal by that laboratory.

Necropsy revealed an excess of depot fat consistent with reported polyphagia often seen with canine insulinoma. The pancreas was slightly smaller than normal and contained a firm 4 mm diameter nodule embedded in the pancreatic tissue. Unfortunately, the lobe in which the nodule was found was not recorded. Histology revealed a large spherical neoplasm with architecture resembling islets of Langerhans. Although unilocular, the neoplasm was considered to be infiltrating surrounding pancreatic tissue.

Case Three

Christy, a spayed female, ten year old Boxer was admitted to SMC with the complaint of weakness and ataxia after exercise for the past year. Christy could usually manage to keep from falling, but had to struggle.

Physical exam revealed a trim subject with no hint of obesity. Blood analysis revealed a mild hypoglycemia (67 mg%) and hypercholesterolemia. When run again the next day, the blood glucose level was lower (55 mg%). Because the hypoglycemia and clinical signs were consistent with insulinoma, a glucagon tolerance test was run the following day. The results were diagnostically positive, however the owners elected not to attempt surgical correction. A blood sample was sent to a private laboratory for the immunoreactive insulin test. It was reported back that insulin levels were 18 micro units/ml.

After three months the owner reported that Christy was leading a very normal life. Due to the winter months, exercise had been somewhat limited and there had been a complete absence of weakness and ataxia. Christy has been on a semi-moist diet all her life which did not seem to affect clinical signs at all.

CONCLUSION

Canine insulinoma should be kept in mind any time a dog is admitted with a complaint of seizures. A fasting blood glucose should be mandatory before automatically putting a dog on anti-convulsive drugs. A clinician may want to see three fasting blood glucose levels at 70-40 mg% or lower before considering a glucagon tolerance test. Although nine blood samples are considered to be needed for an accurate diagnosis, an abbreviated test would be better than none at all should economics so dictate. Samples taken at preinjection, 45 min, 90 min, and 180 min postinjection may give the most valuable information. The entire test, though, is more valid. Early diagnosis is always sought both to give the patient the best chance of survival and to save the client unneeded expense.

At best, the long term prognosis of canine insulinoma is guarded to poor. Owner education is an invaluable aid in deciding what course to follow. Only an owner who is fully aware of the facts can make a decision he will not regret or question in the future.

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BIBLIOGRAPHY